PREPARATION, CHARACTERIZATION AND EVALUATION OF SOLID DISPERSIONS OF ACECLOFENAC- AN ATTEMPT TO DEVELOP FAST RELEASE FORMULATIONS OF SELECTED SOLID DISPERSION OF ACECLOFENAC TABLETS

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CERTIFICATE

This is to certify that the dissertation entitled **"PREPARATION, CHARACTERIZATION AND EVALUATION OF SOLID DISPERSIONS OF ACECLOFENAC - AN ATTEMPT TO DEVELOP FAST RELEASE FORMULATIONS OF SELECTED SOLID DISPERSION OF ACECLOFENAC TABLETS"** *was carried out by* **Mr. YUVARAJU.J,** *in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to the Tamilnadu Dr. M.G.R. Medical University, Chennai, under the direct supervision and guidance of* **Prof. M. Gopal Rao, M.Pharm.,(Ph.D.),** *Department of Pharmaceutics, College of Pharmacy, SRIPMS, Coimbatore.*

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ABBREVIATIONS

ACE	-	Aceclofenac
PVP	-	Polyvinylpyrrolidone
PVA	-	Polyvinyl alcohol
SD	-	Solid Dispersion
PM	-	Physical Mixture
IR	-	Infra Red
DSC	-	Differential Scanning Calorimetry
SE	-	Solvent Evaporation Method
KM	-	Kneading Method
TLC	-	Thin Layer Chromatography

CONTENTS

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PURPOSE OF STUDY

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms[1]. The chain of events that occur following administration of a solid dosage form such as a tablet or a capsule until its absorption into systemic circulation are depicted in below.

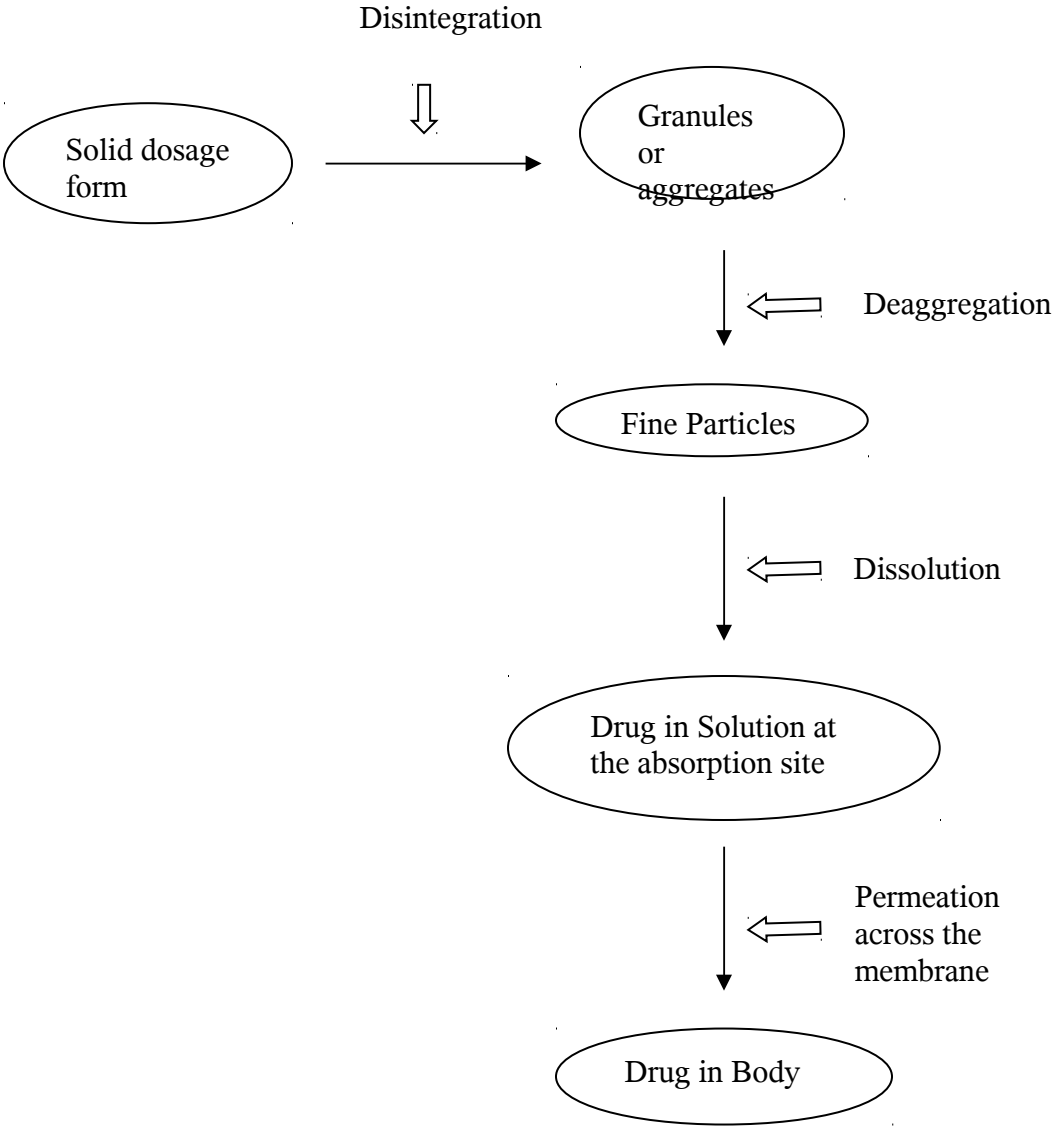


Fig1. Schematic representation of steps involved in the absorption of solid dosage forms

Solid drugs administered orally for systemic activity must dissolve in the gastrointestinal fluids prior to their absorption. Unless the drug goes into solution, it cannot be absorbed into systemic circulation.

Rate Determining Step (RDS): [2]

In a series of kinetic or rate process, the rate at which the drug reaches the systemic circulation is determined by the slowest of the various steps involved in the sequence. Such a step is called as the rate determining or rate limiting step.

Absolute or intrinsic solubility: [2]

It is defined as the maximum amount of solute dissolved in a given solvent under standard conditions of temperature, pressure and p^H. It is a static property**.**

Dissolution rate: [2]

It is defined as the amount of solid substances that goes into solution per unit time under standard conditions of temperature, p^H and solvent composition and constant solid surface. It is a dynamic process.

Several drugs have poor aqueous solubility to have a bearing on dissolution rate. The matter is of great concern when the solubility is less than 1-2 mg /mL in the p^H range of 2-8.

The solubility behavior of drugs remains one of the most challenging aspects in formulation development. With the advent of combinatorial chemistry and high throughput screening, the number of poorly soluble compounds has dramatically increased[3]. The dissolution rate of drug from its dosage form is now considered as an important parameter in the absorption. Dissolution is the rate limiting step in the absorption of drugs from solid dosage form especially when the drug is poorly soluble.

Thus the rate of dissolution of drugs in gastrointestinal fluids could influence the rate and extent of their absorption. In as much as the rate of dissolution of solid is a function of particle size and its solubility in the dissolution medium.[4]An important prerequisite for the absorption of a drug by all mechanisms except endocytosis is that it must be present in aqueous solution. This in turn depends on the drug's aqueous solubility and its dissolution rate.

Effect of particle size reduction:

The stability characteristics of the drug may be altered considerably by reduction of particle size. The resultant increase in surface area places more of the drug molecules in a vulnerable position for rapid degradation by the gastro-intestinal fluids[5].

Particle size reduction is usually achieved by 1.conventional trituration and grinding 2.Ball milling 3.Fluid energy micronization 4.controlled precipitation by change of solvents or temperature, application of ultrasonic waves[6-8] and spray drying 5.administration of liquid solution form which upon dissolution with gastric fluids, and the dissolved drug may precipitate in very fine particles[9]. 6. Administration of water soluble salts of poorly soluble compounds from which from which the parent neutral forms may precipitate in ultra fine from in gastro intestinal fluids.

Although the reduction of particle size can be easily and directly accomplished by the first four methods (1-4), the resultant fine particles may not produce expected faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of the fine particles due to their and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger Vander Wall's attraction between non polar molecules. This was demonstrated by Lin *et al*[10]. Who showed that the invitro dissolution rates of micronized griseofulvin and glutethimide were slower than those of their coarser particles. Further more, drugs with plastic properties are difficult to subdivide by methods 1-3. They have more tendencies to stick together even if fine powders can be produced by controlled precipitation.

The main perspective of the present study aims at overcoming these problems by solid dispersion technology by using carriers like PVP-10, PVP-40, PVP-360 and PVA-8136.With a view to develop fast release formulation of aceclofenac and hence improve its dissolution characteristics. Aceclofenac is an effective NSAID's is practically insoluble in water. Where the dissolution is rate limiting.

The research work envisaged was

1. Literature survey on solid dispersion methods and carriers for solid dispersion.
2. Preparation, characterization and evaluation of solid dispersions of aceclofenac with PVP and PVA.

INTRODUCTION

When the drug is administered in a solid dosage form such as tablet, capsule, or suspension it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. The bioavailability of poorly water soluble drugs is limited by their dissolution rates, which are in turn controlled by the surface area that they are present for dissolution. If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of the drug becomes the rate limiting step in the absorption process, and the particle size of the drug is of great importance in the transport from the gastrointestinal tract to the site of action[11].

Consideration of the modified Noyes-Whitney equation[12,13] provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability:

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

where dC/dt is the rate of dissolution, “A” is the surface are available for dissolution, “D” is the diffusion coefficient of the compound, “Cs” is the solubility of the compound in the dissolution medium, “C” is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions.

Of these possibilities, changes in the hydrodynamics are difficult to invoke in vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the lumenal fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly

encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media[14]. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches.

DEFINITION:

Solid dispersion is defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or the melting-solvent method.

The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The term *coprecipitate* (more accurately *coevaporate)* has also been frequently used when a solid dispersion is prepared by a solvent method.

ADVANTAGES OF SOLID DISPERSIONS:

- Solid dispersion of drugs in solid state is helpful in stabilizing unstable drugs.
- The PEGs may protect certain drug e.g. cardiac glycosides against the decomposition by saliva and allow buccal absorption.
- Solid dispersions may be thermodynamically more active form of drug and directly influence the diffusion and release rate.
- An increased diffusion of steroid from the ointment was obtained.e.g. solid dispersion of prednisolone urea dispersion.
- Solid dispersion technology can be used to solidify liquid drugs.e.g. clofibrate and benzyl benzoate.

DISADVANTAGES OF SOLID DISPERSIONS:

- Tackiness and decommission during preparation and formulation.
- The oral administration of solid dispersions without concomitant reduction in dose may result in higher incidence of adverse effect. E.g. ulceration of indomethacin-PEG 6000 dispersion.
- Difficulty in pulverization of solid dispersion.
- Drug carrier incompatibility.
- Poor flow and mixing properties.
- Sifting of the solid dispersions, which are usually soft and tacky.

CLASSIFICATION OF SOLID DISPERSIONS:

1. Simple eutectic mixtures[15, 16.]

Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of two components in order to obtain a physical mixture of very fine crystals of the two components. When the preparation is dissolved in aqueous medium the carrier will dissolve rapidly, releasing very fine crystals of drug which offers large surface area thereby improvement in dissolution is effected.

2. Solid solutions:

Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions [17] and the dissolution rate are determined by the dissolution rate of the carrier. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude. Solid solutions can be classified according to two methods. First, they can be classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

2.2.1. Continuous and discontinuous solid solutions:

2.2.1.1. Continuous solid solutions: In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

2.2.1.2. Discontinuous solid solutions: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited.

2.2.2. Substitutional crystalline, interstitial crystalline and amorphous solid solutions:

2.2.2.1. Substitutional crystalline solid solutions: Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules[18].

2.2.2.2. Interstitial crystalline solid solutions: In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter[19]. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

2.2.2.3. Amorphous solid solutions: In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman[20] were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP),

polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

SOLID DISPERSION TECHNIQUES:

1. Melting or Fusion Method:

The melting or fusion method was first proposed by Sekiguchi and Obi[21] to prepare fast release solid dispersion dosage forms. In this method the physical mixture of drug and the water soluble carrier is heated directly until it is melted. The melted mixture is then cooled and solidified in an ice bath under vigorous stirring. The final mass was crushed, pulverized and sieved. The dispersion can also be cooled through the process of spray congealing using spray drying equipment. The melted material is sprayed onto cold metal surfaces, which forms pellet of the dispersion. This does not require grinding and therefore no alteration of the crystal modification of the drug occurs. E.g. solid dispersion of sulphamethoxazole, acetaminophen, chloramphenicol, tolazamide, steroids.

Advantages:

- Simplicity and economy.
- This method also advantageous for compounds, which do not undergo significant thermal degradation
- Super saturation of a solute or drug in a system can often be obtained by quenching of the melt rapidly from high temperature.

Disadvantages:

- The main disadvantage of the melt method includes thermal degradation, sublimation and polymeric transformation, which can affect the physicochemical properties of the drug including its rate of dissolution.
- The temperature at which the dispersion solidifies affects crystallization rate and may alter both the size of the crystal and hardness of the dispersion. This may result in tacky or glassy and unmanageable dispersions, which will require storage at elevated temperature to facilitate hardening.

2. Solvent Evaporation Method:

This method involves dissolving the drug and carrier in a suitable organic solvent followed by evaporation of the solvent to form solid dispersion involves dissolving the drug and carrier in a suitable organic solvent followed by evaporation of the solvent to form solid dispersion. The mass was then stored in dessicator, pulverized and sieved. removal is accomplished by various means. The most common approach is the application of reduced pressure at a fixed temperature to evaporate the organic solvent. Temperatures of 125^0C for 25 minutes, 115^0C for one hour[22], -5^0c and reduced pressure followed by drying for 12 hours in vacuum have been used[23]. Spray drying is another approach by which solvent removal can be accomplished and it is probably the fastest way of removing solvent[24, 25]. The freeze drying technique is also employed to prepare solid dispersions by removal of aqueous solutions[26, 27]. E.g. solid dispersion of β-carotene-PVP, griseofulvin-PVP and reserpine-deoxy cholic acid.

Advantages:

- The procedure is suitable for drugs that are thermo labile.
- The thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of the organic solvents.
- For aqueous system, frozen temperature can be used to evaporate the solvent, which can enhance the integrity of the drug.

Disadvantages:

- Difficulty in complete removal of solvent.
- Finding a suitable solvent that will dissolve both the drug and carrier is very difficult.
- Plasticization of some polymers such as poly vinyl pyrrolidone has occurred with the use of some solvents.
- It is important that the rate of evaporation of a solvent is controlled so as to control the particle size of the drug. This in turn will affect the rate of dissolution of the drug in the solid dispersion.

3. Fusion-Solvent Method:

In the fusion solvent method, a carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for removal is eliminated. This method is particularly useful for drugs that have high melting points are that are thermo labile. The feasibility of the method has been demonstrated for spironolactone and griseofulvin dispersions in polyethylene glycol 6000(PEG 6000) [28]. E.g. solid dispersion of clofibrate, methyl salicylate, benzyl benzoate.

MECHANISM OF INCREASED DISSOLUTION RATE BY SOLID DISPERSION SYSTEM:

- In the case of glass solutions, and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to both an increase in surface area and solubilization.
- The carrier material as it dissolves may have a solubilization effect on the drug.
- The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution medium. Then should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.
- Formation of metastable dispersion that has a greater solubility would result in faster dissolution rates.

APPROACHES TO IMPROVE THE SOLUBILITY OR TO INCREASE THE AVAILABLE SURFACE AREA FOR DISSOLUTION: [3.]

I. Physical modifications:

- Particle size
  - Micronization
  - Nanosuspensions
- Modifications of the crystal habit
- Polymorphs
- Pseudo polymorphs (including solvates)
- Complexation/solubilization
  - Use of surfactants
  - Use of cyclodextrines
- Drug dispersion in carriers
  - Eutectic mixtures
  - Solid dispersions (non-molecular)
  - Solid solutions

II. Chemical modification:

- Soluble prodrugs
- Salts

CARRIERS USED FOR SOLID DISPERSION SYSTEMS: [3]

1. Polyethylene glycols (PEGs)
2. Polyvinylpyrrolidone (PVP)
3. Polyvinyl groups
   - Polyvinyl alcohol (PVA)
   - Crospovidone
   - Polyvinylpyrollidone-polyvinylacetate copolymer (PVP-PVA)
4. Cellulose derivatives
   - Hydroxypropylmethylcellulose (HPMC)
   - Hydroxypropylcellulose (HPC)

- Carboxymethylethylcellulose (CMEC)
- Hydroxypropylmethylcellulose phthalate (HPMCP)

5. Polyacrylates and polymethacrylates
   - Eudragit E
   - Eudragit L
6. Urea
7. Sugar, polyols and their polymers
   - Dextrose
   - Sucrose
8. Emulsifiers
   - Sodium Lauryl Sulphate
   - Tween 80
9. Organic acids and their derivatives
   - Succinic acid
   - Citric acid
10. Other carriers
    - Phospholipid
    - Pentaerythritol

NON – STEROIDAL ANTI-INFLAMMATORY DRUGS[30]

Non- Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most widely used for all therapeutic agents. They are frequently prescribed for 'rheumatic' musculoskeletal complaints and are often taken without prescription for minor aches and pains.

NSAIDS include a variety of different agents of different chemical classes. Most of these drugs have three major types of effect.

- Anti-inflammatory effects: Modification of the inflammatory reaction.
- Analgesic effect: reduction of certain sort of pain
- Antipyretic effect: lowering of a raised temperature.

In general, all of these effects are related to the primary action of the drugs-inhibition of arachidonate cyclooxygenase (COX) and thus inhibition of the production of prostaglandins and thromboxanes, though some aspects of the action of individual drugs may occur by different mechanisms.

ANTIPYRETIC EFFECTS

Normal body temperature is regulated by a centre in the hypothalamus which ensures a balance between heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic 'thermostat' that leads to the set point of body temperature being raised. NSAIDs reset the thermostat. The mechanisms of the antipyretic action of the NSAIDs are thought to be due largely to inhibition of prostaglandin production in the hypo-thalamus.

ANALGESIC EFFECT

NSAIDs are mainly effective against pain associated with inflammation or tissue damage because they decrease production of the prostaglandins that sensitive nocicepters to inflammatory mediators such as bradykinin. Therefore they are effective in arthritis, bursitis, pain of muscular and vascular origin, toothache, dysmenorrhoea, the pain of postpariem states and the pain of cancer metastasis in bone, all conditions that are associated with increased prostaglandin synthesis. There is some evidence that they have a central effect by an action mainly in the spinal cord.Clinical data indicate that certain NSAIDs are effective in the control of some types of severe pain unrelated to inflammation.

ANTI – INFLAMMATORY EFFECT:

Drugs such as the NSAIDs reduce mainly those components of the inflammatory and immune response in which the products of COX-2 action play a significant part, namely:

- Vasodilatation
- Oedema
- Pain

COX inhibitors, per se, have no effects on those processes that contribute to tissue damage in chronic inflammatory conditions such as rheumatoid arthritis, vasuclitis and nephritis. Infact, because some prostaglandins decrease lysosomal enzyme release reduces the generation to toxiz O2 products inhibit lymphocyte activation, NSAIDs could actually exacerbate tissue damage in the long term.

CLASSFICATION OF NSAIDS: [31]

The various analgesic –antipyretic anti-inflammatory agents are classified as

1. Acidic Drugs

a. Salicylates:

E.g. Salicylic acid, Apirin

b. Para-amino phenols:

Eg:Paracetamol

c. Pyrazolones:

Eg: Phenylbutazone, Suxibuzone

d. Indole acetic acids:

Eg:Indomethacin, clamidoxic acid

e. Propionic acids:

Eg: Ibuprofen, Diclofenac

f. Aryl anthranilic acids:

Eg: Meclofenamic acid, Tolfenamic acid

g. Miscellaneous agents:

Eg: Piroxicam, Fenoxicam

2. Basic Drugs

Eg: Timegadine, inhibits neutrophil degranulation and superoide production

3. Non-Acidic Drugs:

Eg: Indoxole Nictimodole

CLASSIFICATION OF NSAID'S BY CHEMICAL STRUCTURE:

1. Carboxylic Acid Groups:

- Salicylates (Acetylsalicylate, Choline Salicylate, Diflunisal, Magnesium choline Salicylate, Magnesium Salicylate, Salsa late)
- Acetic Acids (Diclofenac sodium, Diclofenac potassium, Etodolac, Indomethacin, Ketorolac, Nabumetone, Sulindac, Tolmetin)
- Propionic acids (Carprofen, Fenoprofen, Flubiprofen, Ibuprofen, Ketoprofen, Loxoprofen, Naproxen, Naproxen sodium, Oxaprozin, Vedaprofen)
- Anthranilic acids (Meclofenamic acid, Meclofenamate sodium,Tolfenamic acid)
- Phenylacetic acids (Acetaminophen)
- Amino nicotinic acids (Flunixin)
- Indole Analogs (Indomethacin, Nabumetone, Ketorolac, Etodolac,)

2. Enolic Acid Groups (which doesn't have carboxylic group but acid due to the enolic Hydroxy substituent)

- Pyrazolones (Phenylbutazone, Oxyphenbutazone, Dipyrone, Ramifenazone)
- Oxicams (Aceclofenac, Piroxicam, Tenoxicam)

3. Coxibs: Celecoxib, Rofecoxib, Vladecoxib, Parecoxib, Etoricoxib

4. Gold Salts: Auranofin, Gold sodium thiomalate, Aurothioglucose

MECHANISM OF ACTION

The main action of NSAIDs is inhibition of arachidonate cyclo oxygenase. COX is a bifunctional enzyme, having two distinct activities, the main cyclo-oxygenase action which gives PGG2, and a peroxidase action which converts PGG2 to PGH2. Different NSAIDs inhibit the enzyme by different mechanisms.

BIOSYNTHESIS OF PROSTAGLANDINS:

The biochemical effect of NSAIDs includes inhibition of lysosomal membrane stabilization, inhibition of the biosynthesis of mucopolysaccharides, uncoupling oxidative phosphorylation, fibrinolytic activity, sulfahydryl disulfide stabilization. Collagenase production and at times suppression of lymphocytic functions.

Cyclooxgenase catalyses two enzymatic process:

- The incorporation of oxygen in a dioxygenase step to form PGG2 and
- The subsequent peroxidation to PGH2. The reaction is initiated by the stereospecific abstractin of hydrogen at C_{13} followed by oxygen attach at C_{11} and C_{15}.
- Most of NSAIDs act by inhibiting cyclooxygenase by preventing the abstractin of hydrogen from C_{13} and therefore peroxidatin at C_{11} and C_{15}.

Prostaglandins potentiate the early inflammatory response causing vasodilatation, increases permeability, facilitating cellular infiltration land sensitizing the pain receptors to bradykinin. The NSAIDs inhibit both the synthesis and release of prostaglandins.

ADVERSE EFFECTS: [31]

1. **Side effect that occurs at analgesic dose (0.3-1.5g/day)**

   Nausea, vomiting, epigastric distress, increased occult blood loss in stools. The most important adverse effect of NSAIds is gastric mucosal damage and peptic ulceration.

2. **Hypersensitivity and idiosyncrasy**

   Though infrequent, there can be serious reactions, which include rashes, urticaria, rhinorrhea, angiodema, asthama and anaphylactic reaction. Profuse gastric bleeding occurs in rare instance.

3. **Anti – inflammatory dose (1-2g/day)**

   It will produce the syndrome called salicylism- dizziness, tinnitus, vertigo, reversible impairment of hearing and vision, excitement and mental confusion, hyperventilation and electrolyte imbalance.

4. **Gastric Mucosal Damage**

   All NSAIDs to varying extent produce gastric pain, mucosal erosion or ulceration and blood loss.

5. **Renal effect**

   Conditions leading to hypovolemia, decreased renal perfusion and Na^+ loss induce renal prostaglandin synthesis which brings about intra renal adjustment by promoting vasodilation, inhibiting tubular reabsorption and opposing ADH action.

Table.1 Solid dispersion of therapeutic agents

Drug	Carriers	Method	Type of solid dispersion	Effect of dissolution rate
Allopurinol	PVP	S	Not studied	Increased
Benzybenzoate	PEG 6000	MS	Not studied	Increased
Chloramphenicol	Urea	M	Solid solution	Increased
Clofibrate	PEG 6000	MS	Not studied	Increased
Corticosteroids	Sugars	M	Not studied	Increased
Diazepam	PEG 4000	M	solid solution	Not studied
Griseofulvin	Succinic Acid	M	Solid solution	Increased
	PVP	S	Not studied	Increased
	PEG- 4000	MS	Not studied	Increased
	PEG- 6000	M,S	Not studied	Increased
	PEG 2000	M	Not studied	Increased
	Citricacid	M	Glass suspension	Increased
Indomethacin	PEG 6000	M	Not studied	Increased
Methylsalicylate	PEG 6000	S	Not studied	Increased
Paracetamol	Urea	M	Solid solution	Increased
Mannitol	M	Eutetic	Increased	
Primidone	Citric acid	M	Glass solution	Increased
Reserpine	PVP	S	Not studied	Increased
Sulfathiazole	Urea	M	Simple eutectic	Not studied
Tobultamide	PEG- 4000	S	Not studied	Increased
	PEG-6000	S	Not studied	Increased
	PEG4000	M,S	Not studied	Increased
	PEG-2000	M,S	Mono acetic	Not studied
	PVP	S	Not studied	Increased
	PEG-8000	M,S	Not studied	Increased
	PVP	S	Not studied	Increased
	PEG-6000	S	Not studied	Increased
	PEG-4000	M	Not studied	Increased

*M-Melting Method S- Solvent Method MS- Melting solvent method

DRUG PROFILE[32]

Aceclofenac:

Aceclofenac is from the class of Non Steroidal Anti Inflammatory Drug (NSAID), related to diclofenac. It is a derivative of aryl acetic acid.

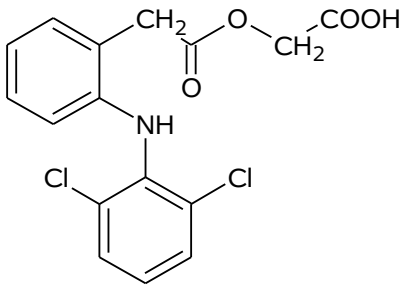
Chemical name: [33]

[[[2-[(2, 6-dichloro phenyl) amino] phenyl] acetyl] oxy] acetic acid.

Empirical formula: [33]

$C_{16}H_{13}Cl_2NO_4$

Chemical Structure: [33]



Characteristics: [34]

White or almost white, crystalline powder. Practically insoluble in water, freely soluble in acetone, soluble in alcohol. Melting point is 149°-150°C.

Pharmacology:

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo oxygenase (COX), which is involved in the production of prostaglandins. Aceclofenac has been shown to exert effect on a variety of mediators of inflammation. The drug inhibits synthesis of the inflammatory cytokines interleukin (IL)-1β and inhibits prostaglandin E_2 (PGE_2) production Invitro data indicate inhibition of COX 1&2 by aceclofenac in whole blood assays; with selectively COX 2 is evident.

In contrast to some other NSAIDs aceclofenac has shown stimulatory effect on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit (IL) - 1β activity. There is also evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli and that 4'-hydroxyl aceclofenac has chondro protective properties attributable to suppression of (IL) - 1β mediated promatrix metallo proteinase production and proteoglycan release.

In patients with osteoarthritis of the knee, aceclofenac decreases pain, reduces diseased severity and improves the functional capacity of the knee. It reduced joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain intensity are reduced and spinal motility improved, by aceclofenac in patients with ankylosing spondylitis.

Pharmacokinetics:

Aceclofenac is rapidly and completely absorbed after oral administration. Peak plasma concentration is reached 1-3 hours after an oral dose. The drug is highly protein bound (>99%). The presence of food does not alter the extent of absorption of aceclofenac but the absorption rate is reduced. The plasma concentration of aceclofenac was approximately twice that in synovial fluid and multiple doses of drug in patients with knee pain and synovial fluid effusion.

Aceclofenac is metabolized to a major metabolite, 4'- hydroxyl aceclofenac and to a number of other metabolites including 5-hydroxy aceclofenac, 4'- hydroxyl diclofenac, diclofenac and 5- hydroxyl diclofenac. These other metabolites account for the fate of approximately 20% of each dose of aceclofenac. Renal excretion is the main route of elimination of aceclofenac with 70-80% of an administered dose found in the urine, mainly as the glucuronides of aceclofenac and its metabolites. Of each of dose of aceclofenac, 20% is excreted in the faeces. The plasma elimination half life of the drug is approximately 4 hours.

Indications:

Aceclofenac is indicated for the relief of pain and inflammation associated with rheumatoid arthritis, oesteo arthritis is ankylosing spondylitis.

Contraindications:

Aceclofenac should not be administered to patients hypersensitive to aceclofenac or other NSAID's, or patients with history of aspirin or NSAID's related allergic or anaphylactic reactions or with peptic ulcers or GI bleeding, moderate of severe renal impairment.

Drug interactions:

Drug interactions associated with aceclofenac are similar to those observed with other NSAID's. Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anti coagulants, inhibit activity of diuretics, enhance cyclosporine nephrotoxicity and precipitate convulsions when co administered with quinolone antibiotics. The co administration of aceclofenac with other NSAID's or corticosteroids may result in increased frequency of adverse events.

Adverse drug reactions:

Aceclofenac is well tolerated with most adverse events being minor and reversible and affecting mainly the GI system. Most common events includes dyspepsia, and abdominal pain, dizziness, vertigo, pruritus, rash and dermatitis have been reported with aceclofenac, but the incidence of these events is less than 5%. Increases blood urea nitrogen and blood creatinine levels have also been reported with aceclofenac treatment. As with other NSAID's, aceclofenac can elevate circulating levels of hepatic enzymes.

Dose and Administration:

The usual dose of aceclofenac is 100mg given twice daily by mouth. One tablet in the morning and one in the evening. There is some evidence that the dose of aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100mg be used.

POLYMER PROFILE [35]

POLY VINYL PYRROLIDONE

1. Non proprietary names:

BP: Povidone

JP: Povidone

Ph Eur: Povidonum

USP: Povidone

2. Synonyms:

E1201; Kollidon: plasdone; PVP: Poly [1-(2-oxo-1- pyrrolidinyl) ethylene]; polyvidone; 1-vinyl-2- pyrrolidionone polymer

3. Chemical name:

1-Ethenyl-2-pyrrolidinone homo polymer

4. Empirical formula:

$(C_6H_9NO)_n$

5. Molecular weight:

2500-3,000,000

Table .2 Approximate molecular weights for different grades of povidone

K value	Approximate molecular wt
12	2500
15	8000
17	10,000
25	30,000
30	50,000
60	400,000
90	1,000000
120	3000000

6. Functional category:

Disintegrant, dissolution aid, suspending agent, tablet binder.

7. Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres.

8. Typical properties:

Acidity/alkalinity : pH = 3.0-7.0 (5% w/v aqueous solution)

True density : 1.180g / cm^3

Melting point : softens at 150°C

Moisture content : Povidone is very hygroscopic significant amounts of moisture. being absorbed at low relative humidities

9. Solubility:

Freely soluble in acids, chloroform, ethanol, ketones, methanol and water, practically insoluble in ether, hydrocarbons and mineral oil.

10. Stability and storage conditions:

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130°C. Steam sterilization of aqueous solution does not alter its properties.

11. Safety:

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.[29]

12. Application in pharmaceutical formulation or technology:

i. It is primarily used in solid-dosage forms.

ii. In tableting, povidone solution are used as binders in wet granulation processes.

iii. It is also added to powder blends in the dry from and granulated inside by the addition of water, alcohol or hydro alcoholic solutions.

iv. It is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid dosage forms.

v. Used as a suspending, stabilizing or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

vi. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

vii. Special grades of pyrogen-free povidone are available and have been used in parenteral formulations.

POLYVINYL ALCOHOL

1. **Nonproprietary Names**

   USP: Polyvinyl alcohol

2. **Synonyms :**

   Airvol; Elvanol; Gohsenol; PVA; vinyl alcohol polymer.

3. **Chemical Name:**

   Erhenol, Homopolymer

4. **Empirical Formula :**

   $(C_2H_2O)_n$

Polyvinyl alcohol is water – soluble synthetic polymer represented by the formula $(C_2H_2O)_n$ The value of n for commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20000-200 000.

Table .3 Commercially available grades of polyvinyl alcohol.

Grade	Molecular weight
High viscosity	~ 200 000
Medium viscosity	~ 130 000
Low viscosity	~ 20 000

5. Molecular Weight:

(20 000 -200 000)

6. Functional Category:

Coating agent; lubricant; stabilizing agent; viscosity –increasing agent.

7. Description:

Polyvinyl alcohol occurs as an odorless, white to creamcolored granular powder.

8. Typical Properties:

Melting point:

- 228℃ for particularly hydrolyzed grades
- 180-190 C for partially hydrolyzed grades

Refractive index:

N25/D = 1.49-1.53

Solubility:

Soluble in water; insoluble in organic solvents.

Specific gravity:

1.19-1.31 for solid at 25℃

1.02 for 10% w/v aqueous solution at 25℃

Specific heat:

1.67 J/g (0.4 cal/g)

Table .4 Viscosity of polyvinyl alcohol:

Grade	Dynamic viscosity of 4% w/v aqueous solution at 20℃ (mPas)
High viscosity	40.0-65.0
Medium viscosity	21.0-33.0
Low viscosity	4.0-7.0

9. Stability and Storage Conditions:

Polyvinyl alcohol is when stored in a tightly sealed Polyvinyl in a cool, dry place. Preservatives may be in added to the solution if extended storage is required. Polyvinyl alcohol undergoes slow degradation at 100℃ rapid degradation at 200℃. It is stable on exposure to light.

10. Safety:

Poly vinyl Alcohol is generally considered a non toxic material. It is non irritant to the skin and eyes concentrations up to 10% concentrations up to 7% are used as cosmetics.

REVIEW OF LITERATURE

- Franco *et al.,* [36] (2001) have studied dissolution properties and anticonvulsant activity of phenytoin-polyethylene glycol 6000 and polyvinylpyrollidone K-30 solid dispersions with different drug to carrier ratios were prepared by the solvent method. Among the various ratios, drug solubility and dissolution rate are improved by these formulations, particularly with SDPEG 1/20 and SDPVP 1/20 systems. Storage was found to influence the stability of the solid dispersions. . By maximal electroshock test, it was found that the intraperitoneal administration in mice of the SDPEG 1/20 and SDPVP 1/20 systems exhibited anticonvulsant activity similar to diphenylhydantoin sodium salt.

- Kazunari *et al.* [37], (2003) have established new preparation method for solid dispersion formulation of tacrolimus using three different carriers like polyethylene glycol 6000 (PEG 6000), polyvinylpyrollidone (PVP) and hydroxypropylmethylcellulose (HPMC) were prepared by the conventional solvent method, in which tacrolimus and the carrier was completely dissolved in the mixture of dichloromethane and ethanol. In new method solid dispersion of tacrolimus was prepared without using dichloromethane as a solvent. The in vivo oral absorption study in dogs showed that bioavailability of tacrolimus from SDF with HPMC was remarkably improved compared with the crystalline powder. It was clarified that HPMC is the most appropriate carrier for SDF of tacrolimus. The physicochemical properties of SDF with HPMC prepared by the new method were the same as those of SDF prepared by the conventional solvent method. They concluded the pharmacokinetic parameters after oral administration in monkeys showed no significant difference (P >0.01) between solid dispersion s with HPMC prepared by the two methods.

- Anant *et al.* [38], (2004) were characterized solid dispersion of cur cumin–PVP obtained by spray drying they revealed the changes in solid state during the formation of dispersion by physical characterization studies and also solid dispersion showed

complete dissolution with in 30 minutes. This in turn may aid in improving bioavailability and dose reduction of the drug.

- Sethia and Squillante[39] (2004) were prepared solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. They have suggested that the best intrinsic dissolution rate (IDR) was obtained for super critically processed CBZ/PVP K30 that was four-fold higher than pure CBZ and the supercritical-based process produced solid dispersions with IDR better than conventional solid dispersions augmented with amphiphilic carriers.

- Susumu *et al.,*[40] (2005) studied the effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method. The apparent crystallinity of troglitazone in the SDs decreased with increase in water content in the PM. In particular, SDs prepared by heating at 130 and 150℃ showed 0% apparent crystallinity when the water content in the PM were more than 13 and 8%, respectively. When the heating temperature used was higher than the glass transition temperature of PVP plasticized with water, troglitazone crystals were dissolved in the rubbery PVP. Therefore, even if the heating temperature is lower than the melting point of troglitazone during preparation, controlling the water content in the PM at a high level can produce a troglitazone SD with 0% apparent crystallinity.

- Masayasu *et al.,* [41] (2005) have studied the inhibition of a solid phase reaction among excipients that accelerates drug release from a solid dispersion with aging. A modified release product of a therapeutic drug for hypertension, Barnidipine hydrochloride, was developed. The drug product consisted of solid dispersion based on a matrix of carboxymethylethylcellulose (CMEC), which was produced using the spray-coating method. The molecular bases of dissolution of the drug substance from those matrices were investigated. The molecular weight of CMEC was found to be a dominant factor that determined dissolution kinetics, which followed zero-order release, suggesting an involvement of an osmotic pumping mechanism. The solid phase reaction advanced differentially in the solid dispersion depending on the degree

of phase separation set initially. The use of non-aqueous solvents and/or a decrease in the coating temperatures inhibited the occurrence of phase separation upon production, thereby preventing the formation of CMEC-rich phases where the solid phase reaction occurred during storage.

- Toshio *et al.,* [42] (2005) were investigated the release mechanism of poorly water-soluble drug from the extended release solid dispersion systems with water insoluble ethyl cellulose (EC) and water soluble hydroxypropylmethylcellulose (HPMC) (1:1). Indomethacin (IND) was used as a model of poorly water-soluble drug. The dissolution behavior of IND depended on the structures of EC–HPMC matrices, which were overned by the preparation method. In addition, the dissolution behavior showed pH dependency that the dissolution rate of IND was slower in acidic medium than that in neutral medium. The experimental results revealed that the hydrophobic interaction between IND and EC occurred under lower pH and strongly delayed the dissolution rate of IND. The relationship between this hydrophobic interaction and the dissolution rate of IND was also proposed.

- Hirofumi *et al.,* [43] (2005) was prepared the solid dispersion particles of indomethacin (IMC) with different types of silica, non-porous (Aerosil 200) or porous silica (Sylysia 350) by using spray-drying method. In comparing the effect of the type of the silica particles, the dissolution rate of solid dispersion particles with Sylysia 350 was faster than that with Aerosil 200. The formulation amount of IMC did not affect on the amorphous state of IMC in the resultant solid dispersion particles in powder X-ray diffraction patterns. The dissolution rate of IMC from the solid dispersion particles with Sylysia 350 was faster than that of Aerosil 200 irrespective of IMC content. In stability test, amorphous IMC in the solid dispersion particles with each silica particles did not crystallize under storing at severe storage conditions (40℃, 75% RH) for 2 months, while amorphous IMC without silica easily crystallized under same conditions.

- Jingjun *et al.,* [44] (2006) were elucidate the controlled-release mechanism of a poorly water-soluble drug from microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend prepared by a phase-separation method, nifedipine-loaded microparticles with different levels of drug loading were evaluated by micromeritic properties, drug physical state, matrix internal structure, drug dissolution, and release modeling. Moreover, study results indicated that even though drug loading did not significantly affect the microparticle size distribution and morphology, nifedipine release rate from those microparticles was more or less influenced by the level of drug loading, depending on matrix formulation. At higher levels of drug loading, probably due to formation of solid nifedipine domains in microparticles, a change in the release kinetics was observed.

- Drooge *et al.,* [45] (2006) were characterized the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. The molecular distribution in fully amorphous solid dispersions consisting of poly(vinylpyrrolidone) (PVP)–diazepam and inulin–diazepam was studied. One glass transition temperature (*T*g), as determined by temperature modulated differential scanning calorimetry (TMDSC), was observed in PVP–diazepam solid dispersions prepared by fusion for all drug loads tested (10–80 wt.%). These observations indicate that diazepam was dispersed in PVP on a molecular level. However, in PVP–diazepam solid dispersions prepared by freeze drying, two *T*g's were observed for drug loads above 35 wt.% indicating phase separation. One *T*g indicated the presence of amorphous diazepam clusters, the other *T*g was attributed to a PVP-rich phase in which diazepam was dispersed on a molecular level. Water vapour sorption (DVS) experiments revealed that the PVP-matrix was hydrophobised by the incorporated diazepam. TMDSC and DVS results were used to estimate the size of diazepam clusters in freeze dried PVP–diazepam solid dispersions, which appeared to be in the nano-meter range. The inulin–diazepam solid dispersions prepared by spray freeze drying showed one *T*g for drug loads up to 35 wt.% indicating homogeneous distribution on a molecular level. For higher drug loads, a *T*g of diazepam as well as a *T*g of the inulin-rich phase was observed, indicating the formation of amorphous diazepam clusters.

In contrast to the PVP–diazepam solid dispersions, DVS-experiments revealed that inulin was not hydrophobised by diazepam. Consequently, the size of diazepam clusters could not be estimated. It was concluded that TMDSC enables characterization and quantification of the molecular distribution in amorphous solid dispersions. When the drug reduces the hygroscopicity of the carrier, DVS in combination with TMDSC can be used to estimate the size of amorphous drug clusters.

- Nora[46] (2006) has studied stabilization of solid dispersions of nimodipine using macrogol cetostearyl ether, macrogol glycerol monostearate, polysorbate 60, ceto stearyl alcohol, and glycerol monostearate and sodium lauryl sulphate as well as hydroxypropyl cellulose butylmethacrylat- (2-dimethylaminoethyl) methacrylatmethyl methacrylat-copolymer, polyacrylic acid, polyvinylalcohol and povidone K17 were included in the study.Among these carriers povidone K17 effectively prevents recrystallization in solid solutions containing of nimodipine during storage at +25 ^{0}C over silica gel thereby ensuring a substantial increase in the dissolution rate.

- Eun-Jung et *al.,* [47] (2006) has studied the dissolution rates of felodipine using PVP and HPMC carriers by solvent wetting method. It could be shown that the dissolution rates of felodipine in PVP and HPMC solid dispersion were much faster than those for the corresponding physical mixtures. However, dissolution profiles were found to depend on the carrier used; the dissolution rate of felodipine increased slowly for solid dispersions prepared using HPMC, whereas rapid initial dissolution rates were observed for solid dispersions prepared using PVP or poloxamer. Increases in dissolution rates were partly dependent on the ratios of felodipine to carrier. No significant changes in crystal form were observed by X-ray diffraction or thermal analysis, and no significant changes in dissolution rate were observed when sorbitol and mannitol were used as carriers.

- Ningyun et *al.,* [48] (2007) studied the dissolution enhancement of silymarin- PVP solid dispersion pellets prepared by a one step fluid bed coating technique. They reported that the dissolution rate of silymarin-PVP solid dispersion was enhanced greatly at drug carrier ratio of over 4:1. The results of the central composite design suggested that both PVP/SM ratio and coating weight gain affected the dissolution rate

significantly. Second-order or third-order polynomial non-linear equations were employed to estimate the relationship between dissolution responses and the two independent variables. Response surface graphs were delineated based on the best-of-fit equations and the optimal experimental range was identified as: PVP/SM, 4/1-5/1; coating weight gain, 80%-120%. The results indicate that the fluid-bed coating technique has the potential use in the preparation of solid dispersions.

- Naveen *et al.,* [49] (2007) have studied enhancement of dissolution and mathematical modeling of drug release of a poorly water-soluble drug (rofecoxib) using water-soluble carriers viz. polyethylene glycols (PEG 4000 and 6000), polyglycolized fatty acid ester (Gelucire 44/14), polyvinylpyrollidone K25 (PVP), poloxamers (Lutrol F127 and F68), polyols (mannitol, sorbitol), organic acid (citric acid) and hydrotropes. All the solid dispersions showed dissolution improvement vis-a`-vis pure drug to varying degrees, with citric acid, PVP and poloxamers as the most promising carriers. Solid-state characterization techniques revealed that distinct loss of drug crystallinity in the formulation, ostensibly accounting for enhancement in dissolution rate.

MATERIALS AND METHODS

Table.5 Materials used

Name of the materials	Name of company
Aceclofenac	Anglo-french Drug Industries Limited
PVP 10	Sigma Aldrich Ltd
PVP 40	Sigma Aldrich Ltd
PVP 360	Sigma Aldrich Ltd
PVA 8136	Sigma Aldrich Ltd
Ethanol	Changshu Yangyuan Chemical
Sodium hydroxide	SD fine chem. Ltd
Potassium dihydrogen phosaphate	Ranchem Ltd
Glacial acetic acid	SD fine chem. Ltd
Toluene	Qualigens
Ethyl acetate	SD fine chem. Ltd
Potassium bromide	Qualigens

Table .6 Equipments used:

Name of equipment	Name of company
Vacumm pump	Gelman sciences
Dissolution apparatus	Electoral TDT – 08L
UV spectrometer	Jasco V 530
Alphadigidoc TM	Alpha Innotech corporation
FT IR spectrometer	(Jasco-FT-IR 8201 PC)
pH testr 1 (water proof)	Oakton instruments.

ANALYTICAL METHOD FOR ACECLOFENAC[50]

1. Spectrophotometric method for the estimation of aceclofenac in tablets:

A standard solution containing 1mg/ml of aceclofenac was prepared in methanol by dissolving 50mg of pure drug aceclofenac in 50 ml of methanol. From this solution working atandard solutions of concentrations 0-20mcg/ml of aceclofenac were prepare dby dilution with mwthanol. The absorbance of the solutions was measured at 275nm against reagent blank.

2. Analytical methodology used in the present study:

Procedure for standard graph preparation of aceclofenac

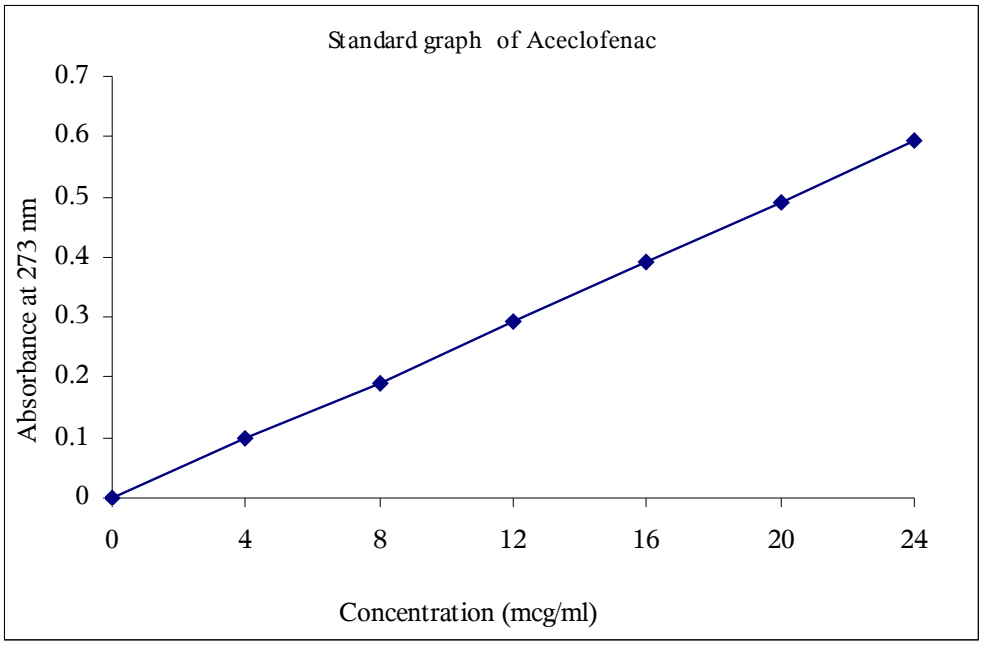
About 10mg of aceclofenac was accurately weighed and dissolved in 100 ml of ethanol. This will give the stock solution of concentration 100mcg/ml.

From this solution pipette out 0.4,0.8,1.2,1.6 2.0 and 2.4 ml, which were transferred into a series of 10ml volumetric flasks and the final volume was brought up to 10ml with pH 7.4 phosphate buffer to get a concentration of 4-24 mcg/ml. A blank was also prepared. The absorbance was measured at 273 nm and the standard graph was plotted against concentration (mcg/ml) Vs absorbance. The results were given in table.7 and figure.2.

Table.7 Standard graph of aceclofenac:

Concentration (mcg/ml)	Absorbance at 273 nm
0	0.000
4	0.093
8	0.199
12	0.294
16	0.391
20	0.490
24	0.592

Fig.2 Standard graph of aceclofenac at pH 7.4 phosphate buffer:


Standard graph of Aceclofenac
Absorbance at 273 nm
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
4
8
12
16
20
24
Concentration (mcg/ml)

EXPERIMENTAL METHODOLOGY

PREPARATION AND CHARACTERIZATION OF ACECLOFENAC SOLID DISPERSION:

Solid dispersion technology can be used to improve the in vitro and in vivo dissolution properties of poorly soluble drugs. Aceclofenac is practically in soluble in water. The dissolution rate from solid dispersion was affected by the carrier concentration. PVP and PVA were used as carriers in the preparation of aceclofenac solid dispersion in the ratios of 1:1, 1:3 and 1:9 by kneading and solvent evaporation method.

Procedure for preparation of aceclofenac solid dispersion by kneading method:

PVP or PVA and solvent were mixed together in a mortar so as to obtain a homogenous paste. Aceclofenac was then added slowly with constant stirring. The mixture was then ground for 1 hour. During this process, an appropriate quantity of solvent was added to the mixture in order to maintain a suitable consistency. The paste was dried in oven at 40℃ for 24 hours. The dried complex was pulverized into a fine power.

Procedure for preparation of aceclofenac solid dispersion by solvent evaporation method

In solvent evaporation method, ethanol was used as solvent and three different drug: carrier ratios were used (1:1, 1:3, 1:9) to prepare solid dispersion of aceclofenac.

Respective amount of carrier was dissolved in required amount of ethanol taken in a conical flask to get a clear completely soluble polymer ethanol solution. Magnetic stirrer was used for this purpose. The weighed amount of aceclofenac was added to this solution carefully with constant stirring. Stirring was continued until the drug was completely incorporated in solvent. Then the solvent was removed by evaporation at 40° C under vacuum. The mass obtained was dried crushed, pulverized and shifted through mesh no. 80.

Physical mixture (PM)

Drug: Carrier ratio of 1:1 was used to prepare physical mixture (1000mg of drug and 1000mg of carrier). The drug and carrier were mixed thoroughly in a mortar. This was done by geometric dilution technique to ensure homogenous distribution.

Table .8 Drug carrier ratio and respective amount taken:

CHARACTERIZATION AND EVALUATION OF ACECLOFENAC SOLID DISPERSION

a. Thin layer Chromatography
b. IR spectral Analysis
c. Powdered X-ray Diffraction studies
d. Differential Scanning Calorimetry
e. Drug content uniformity
f. Invitro dissolution studies

Thin layer chromatography (TLC):

A thin layer chromatographic method was also carried to study the interaction between the drug and carriers and also to confirm the chemical satiability of the solid dispersions prepared. For this, the pure drug and the solid dispersions prepared with various carriers by solvent evaporation method were subjected to chromatographic studies.

The TLC system used for this study is given below.

Precoated TLC Plates : Manufactured by SD Fine chemicals Ltd, Mumbai
Adsorbent Layer : Silicagel GF 254.
Layer Thickness : 250 &μm.
Separation technique : Ascending
Chamber Saturation : The chamber was lined on three sides with filter paper and saturated for 30 minutes.
Mobile phase : Toluene: ethyl acetate: glacial acid [5:5:0.2% v/v]
Preparation of sample : A suitable amount of pure drug or equivalent solid dispersion dissolved in ethanol and used for spotting.

Amount applied : 10 µl.

Detection : Short and long wavelength of light.

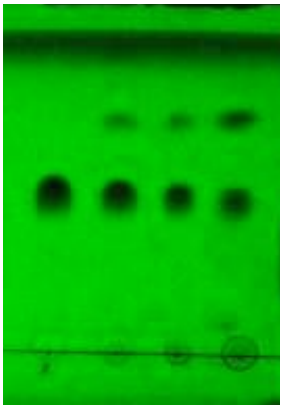
The Rf values obtained were given in the table.9-10 and thin layer chromatograms of various solid dispersions were shown in fig.3-4.

Table. 9 TLC data for various solid dispersions systems (Kneading Method)

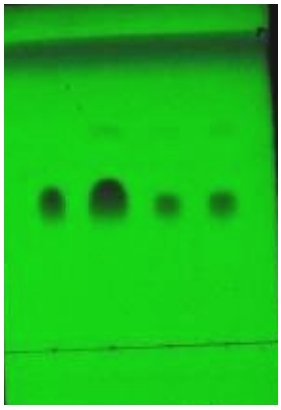
Solid dispersion ratio	Aceclofenac PVP10	Aceclofenac PVP40	Aceclofenac PVP360	Aceclofenac PVP10 PVA8136	Aceclofenac PVP40 PVA8136	Aceclofenac PVP 360 PVA8136
Pure drug	2.04	2.12	2.13	2.00	2.13	2.00
1:1	2.04	2.01	2.04	2.00	2.08	2.04
1:3	2.04	2.02	2.02	2.00	2.10	2.00
1:9	2.04	2.12	2.02	2.00	2.10	2.00

Table. 10 TLC data for various solid dispersions systems (Solvent Evaporation method)

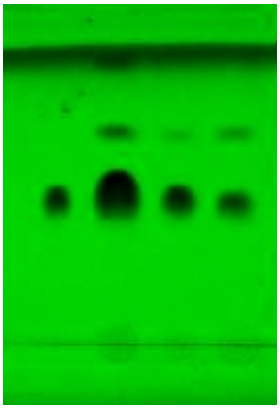
Solid dispersion ratio	Aceclofenac PVP10	Aceclofenac PVP40	Aceclofenac PVP360	Aceclofenac PVP10 PVA8136	Aceclofenac PVP40 PVA8136	Aceclofenac PVP 360 PVA8136
Pure drug	2.00	2.09	2.04	2.08	2.00	2.04
1:1	2.09	2.09	2.04	2.00	2.00	2.04
1:3	2.09	2.09	2.10	2.08	2.00	2.04
1:9	2.09	2.10	2.10	2.08	2.00	2.04



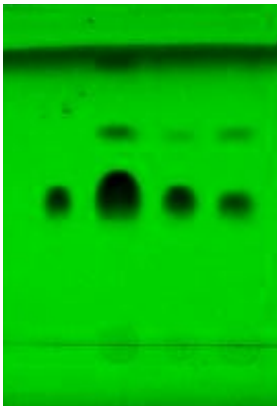
KM PVP 10



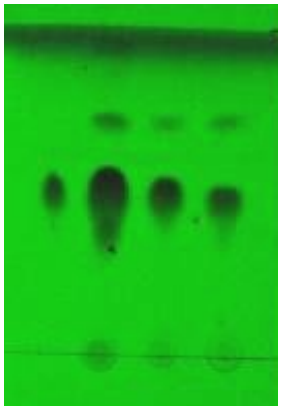
KM PVP360



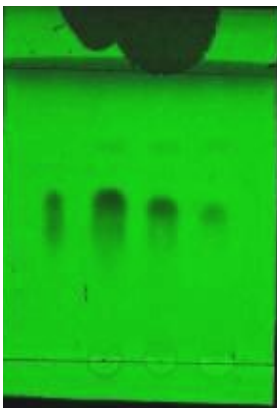
KM PVP40 + PVA8136



KM PVP 40

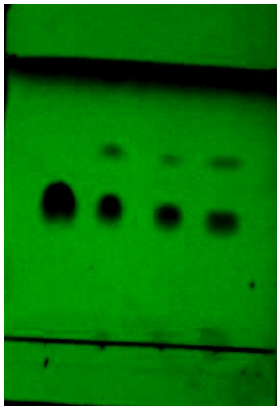


KM PVP 10 +PVA 8136

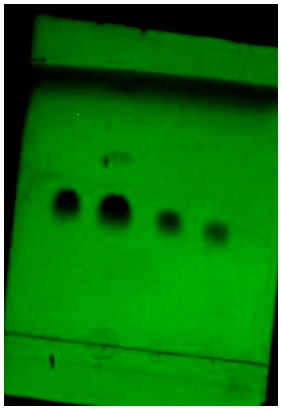


KM PVP360 +PVA 8136

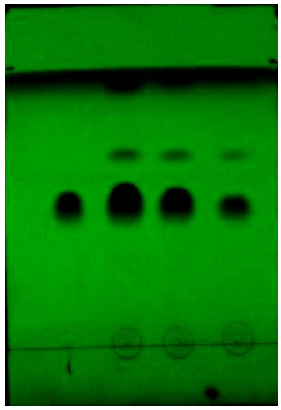
Fig.3 Thin layer chromatogram of various solid dispersions (Kneading method)



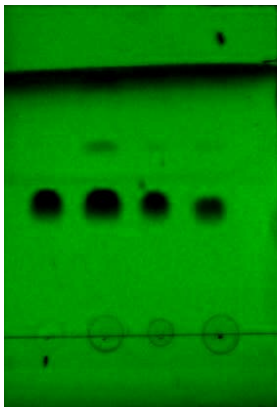
SE PVP10



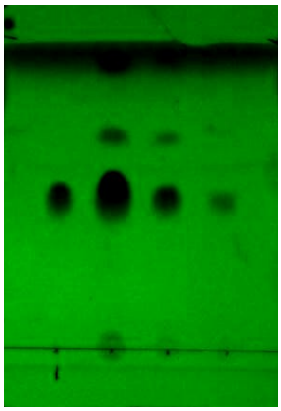
SE PVP360



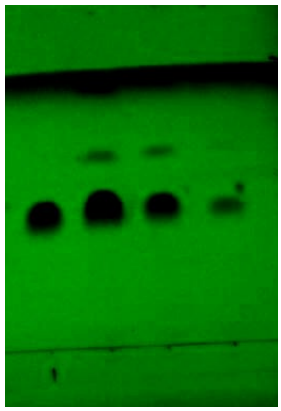
SE PVP 40 PVA8136



SEPVP 40



SE PVP10 PVA8136



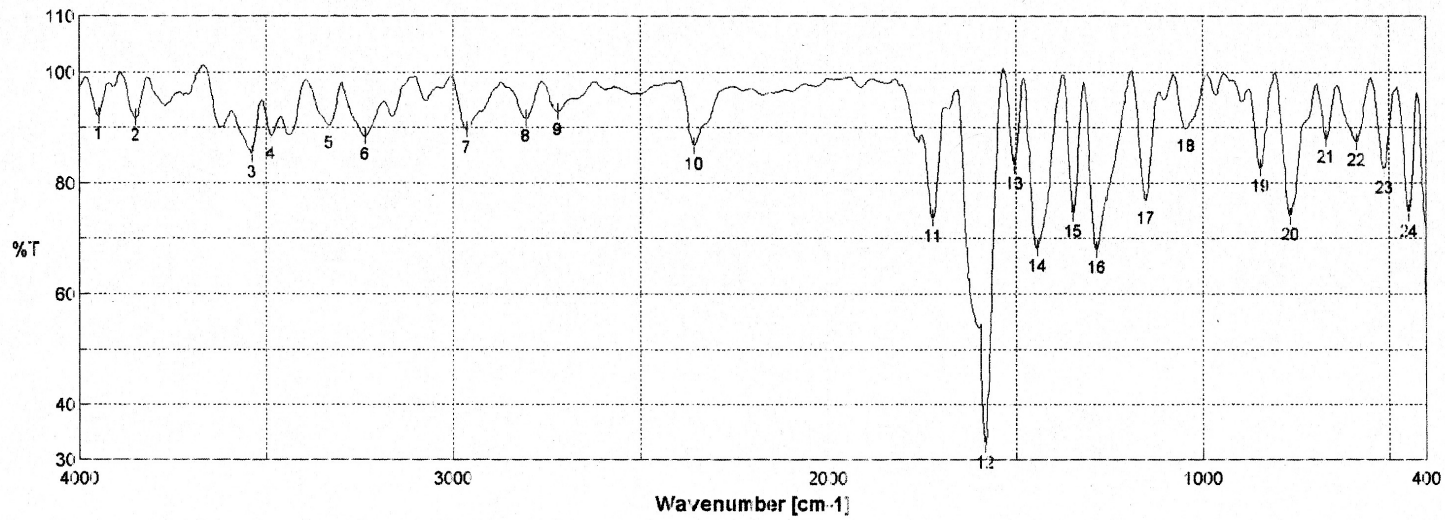
SE PVP360 PVA 8136

Fig.4 Thin layer chromatogram of various solid dispersions (solvent evaporation method)

IR Spectral analysis:

Fourier Transform (FTIR) spectra of the samples were obtained in the range of 400-4000 cm^{-1} using a Jasco-FT-IR 8201 PC Spectrophotometer (Jasco.Essex) by the KBr disc method. The IR Spectra obtained are given in fig. 5-7.

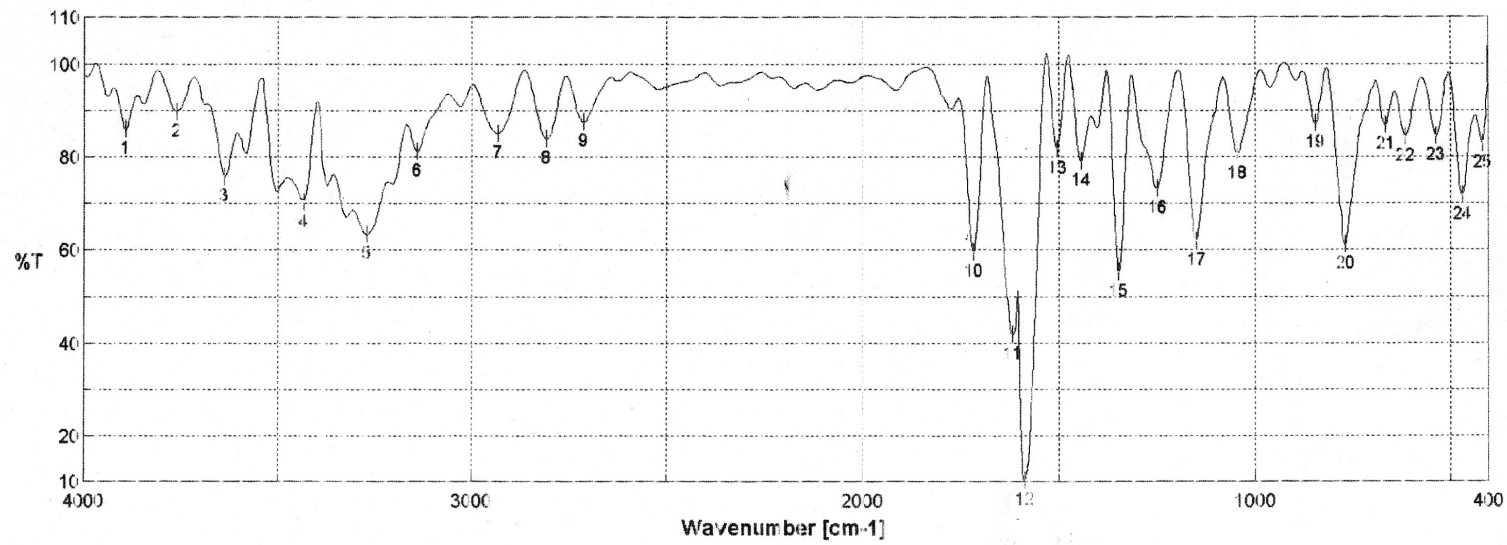
Figure 5: IR spectrum of pure aceclofenac



Accumulation	16	Resolution	4 cm-1
Zero Filling	OFF	Apodization	Cosine
Gain	8	Aperture	7.077 mm
Scanning Speed	2 mm/sec		
Date/Time	10/ 1/2007 11:32AM	Update	10/17/2007 1:53PM
Operator	C.Geetha		
File Name	Memory#19		
Sample Name	KMPVP 401:9		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3947.57	92.0373	2	3847.29	91.7763	3	3538.74	85.1554	4	3486.67	88.5217	5	3330.46	90.5173
6	3237.9	88.4475	7	2962.13	89.561	8	2605.92	91.6145	9	2724.92	92.8976	10	2360.44	86.6694
11	1722.12	73.6137	12	1581.34	32.7664	13	1504.2	83.1411	14	1444.42	68.3321	15	1348	74.5587
16	1284.36	68.0044	17	1149.37	76.3067	18	1043.3	89.9531	19	844.669	82.7013	20	763.673	73.9764
21	665.321	87.902	22	586.254	87.3804	23	512.972	82.3515	24	445.476	74.4763			

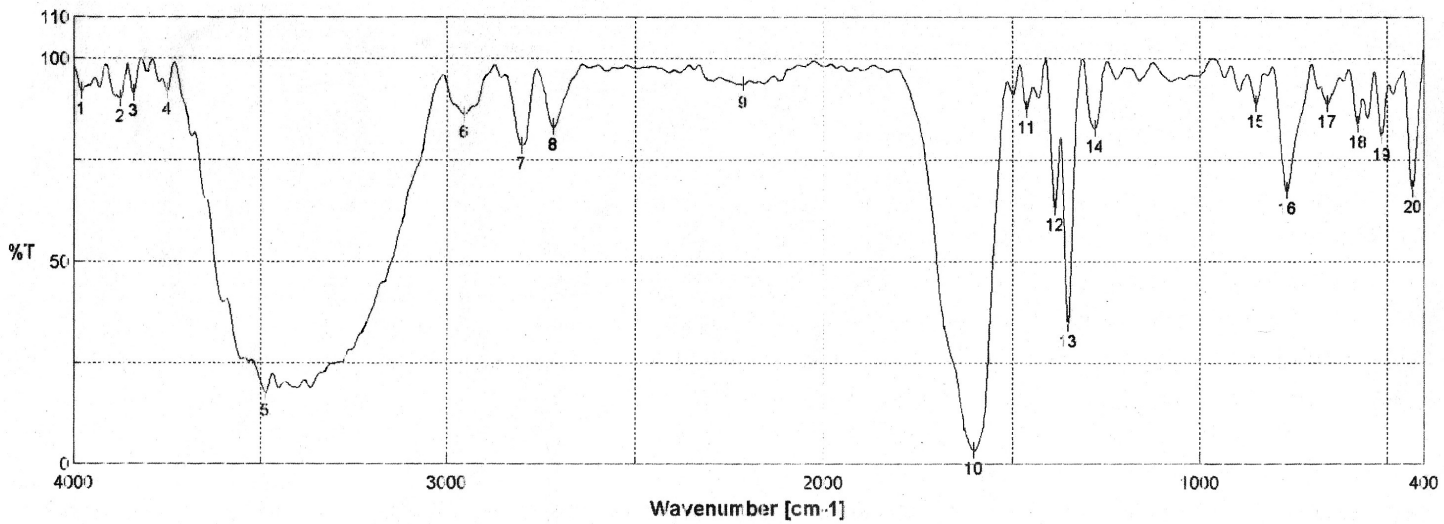
Figure 6: IR spectrum of solid dispersions of aceclofenac with PVP 40 (1:9) KM



Accumulation	16	Resolution	4 cm-1
Zero Filling	OFF	Apodization	Cosine
Gain	16	Aperture	7.077 mm
Scanning Speed	2 mm/sec		
Date/Time	10/10/2007 3:27PM	Update	10/17/2007 1:27PM
Operator	C.Geetha		
File Name	Memory#20		
Sample Name	ACE		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3891.65	85.921	2	3760.51	89.7055	3	3640 95	75.856	4	3432.67	70 2144	5	3272.61	63.3794
6	3143.4	81.1094	7	2935.13	85.0348	8	2611 7	83.8389	9	2717.21	87 563	10	1716.26	59.6184
11	1616.06	41.7024	12	1585.2	10.2852	13	1504 2	81.7406	14	1444.42	79 0652	15	1348	55.249
16	1247.72	73.2998	17	1145.51	61.9775	18	1043 3	80.6711	19	844.669	87 2078	20	765.601	61.1252
21	661.464	86.9311	22	611.324	84.399	23	536.114	84.5078	24	468.617	71 789	25	416.649	82.8433

Figure 6: IR spectrum of solid dispersions of aceclofenac with PVP 40 (1:9) SE



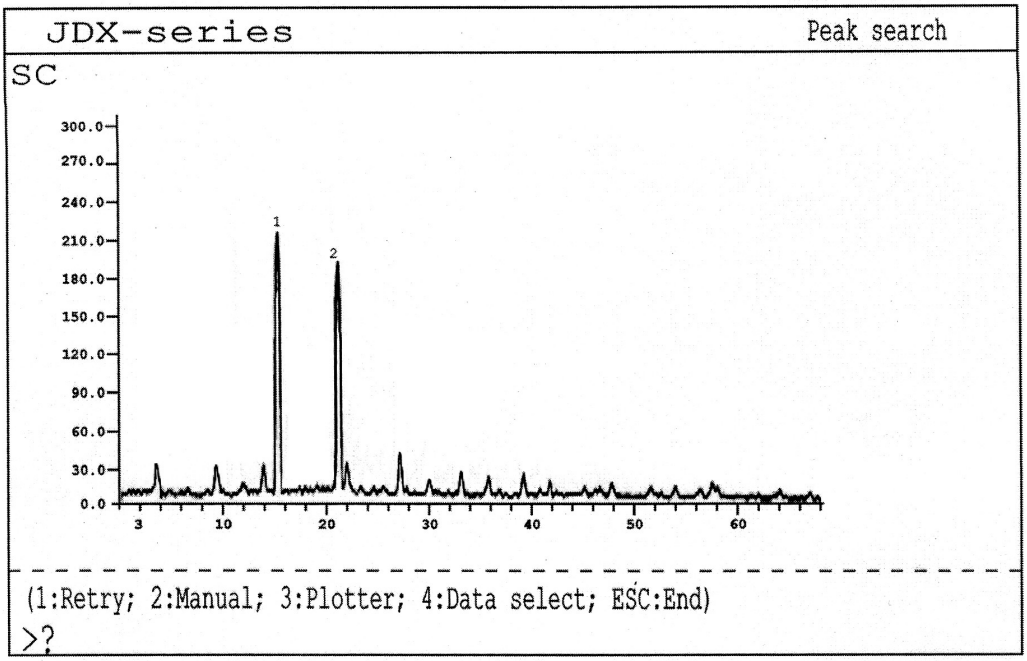
Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	10/12/2007 4:18PM	Update	11/19/2007 10:33AM
Operator	C.Geetha		
File Name	SE pvp40(1:9)		
Sample Name	SE pvp40(1:9)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3979.39	91.9621	2	3877.18	90.145	3	3841.51	91.459	4	3752.8	91.9512	5	3486.67	17.6125
6	2956.34	86.238	7	2804.96	78.4921	8	2719.14	83.0874	9	2210.02	93.5778	10	1599.66	3.44663
11	1461.78	87.5308	12	1383.68	63.3417	13	1348	34.6687	14	1276.35	82.7189	15	848.525	88.8868
16	767.53	67.4121	17	661.464	88.7551	18	579.504	83.7726	19	514.901	80.6596	20	431.977	67.8784

Powder X-ray diffractometry:

The Powder X-ray Diffraction Patterns were recorded using a siemens, Munich, Germany) with Cu as anode material and crystal graphite monochromator, operated at a voltage of 40 KV and a current of 30 MA. The samples were analyzed in the 2θ angle range of 2° to 65° and the process parameters were set as follows: step size of 0.45° (2θ), scan step time of 0.5 seconds and time of acquisition of 2 hours. The results were shown in fig. 8, 9.

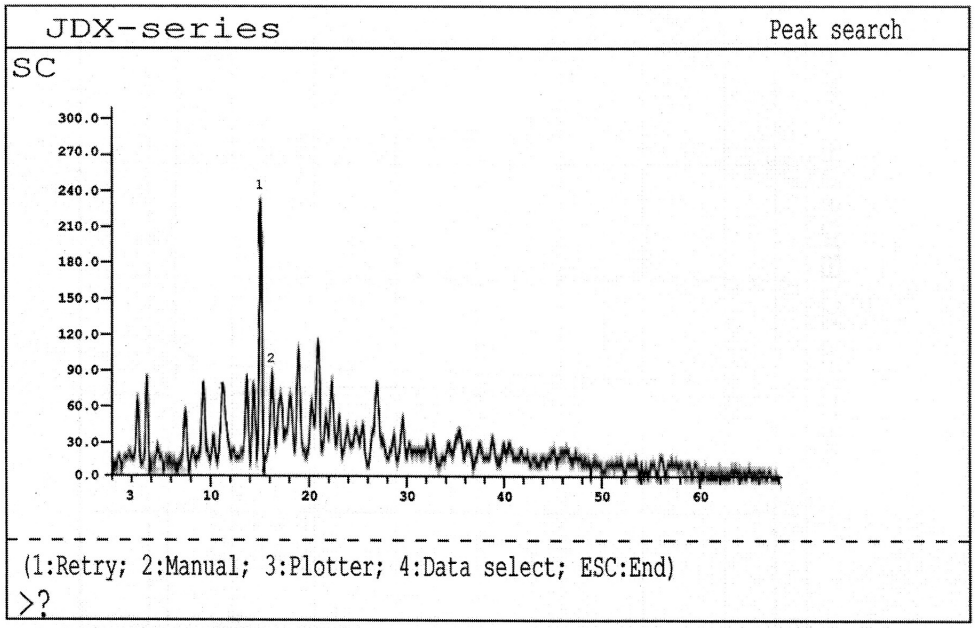
Figure 8 X- ray diffraction studies of pure aceclofenac:



Peak table

Nr.	2θ	d	I	I/Io
1	13.300	3.009	271	58
2	12.000	2.815	223	56

Figure9 X- ray diffraction studies of solid dispersions of aceclofenac with PVP 40 (1:9) KM



Peak table

Nr.	2θ	d	I	I/Io
1	10.600	2.200	205	41
2	13.800	2.014	77	15

Differential Scanning Calorimetry:

The DSC measurements were performed using a Mettleer Toledo DSC 821e DSC module controlled by STARe Software (Mettler – Toledo. GmbH, Switzerland). All accurately weighted samples (1 mg of aceclofenac or its equivalent) were placed in seated aluminum pans, before heating under nitrogen flow (20ml/min) at a scanning rate of 10° C min-1, over the temperature range of 30℃ to 220℃. An empty aluminum pan was used as reference.

The samples were analyzed for aceclofenac after suitable dilution by measuring absorbance at 365 nm using Jasco V-530 UV visible spectrophotometer. Phosphate buffer of pH 7.4 used as blank. The percentage of aceclofenac dissolved at various time intervals was calculated and plotted against time. T_{50}, T_{90} values calculated from these dissolution curves. The results are shown in fig.10-11.

Figure 10 DSC thermogram of pure aceclofenac

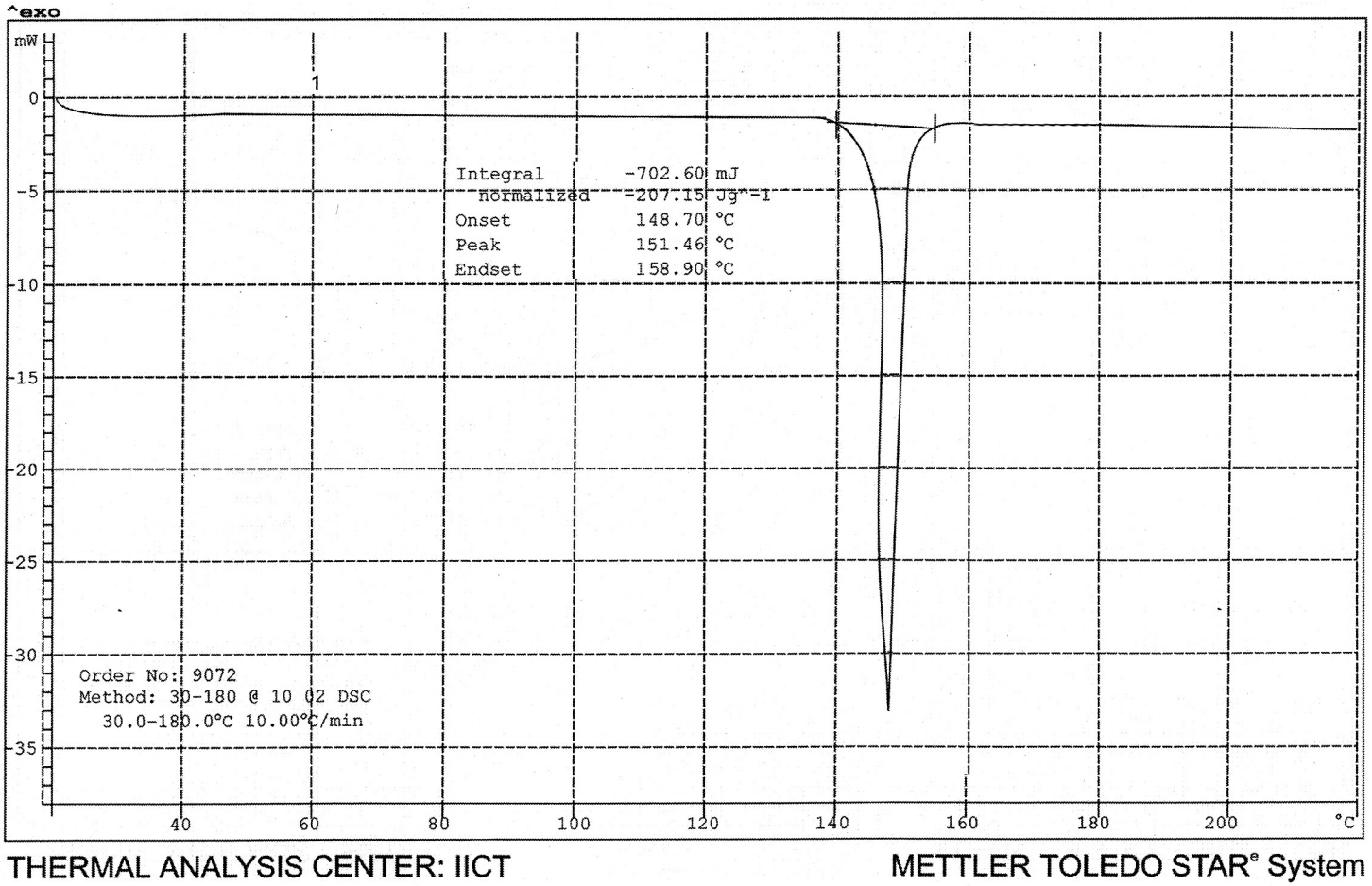
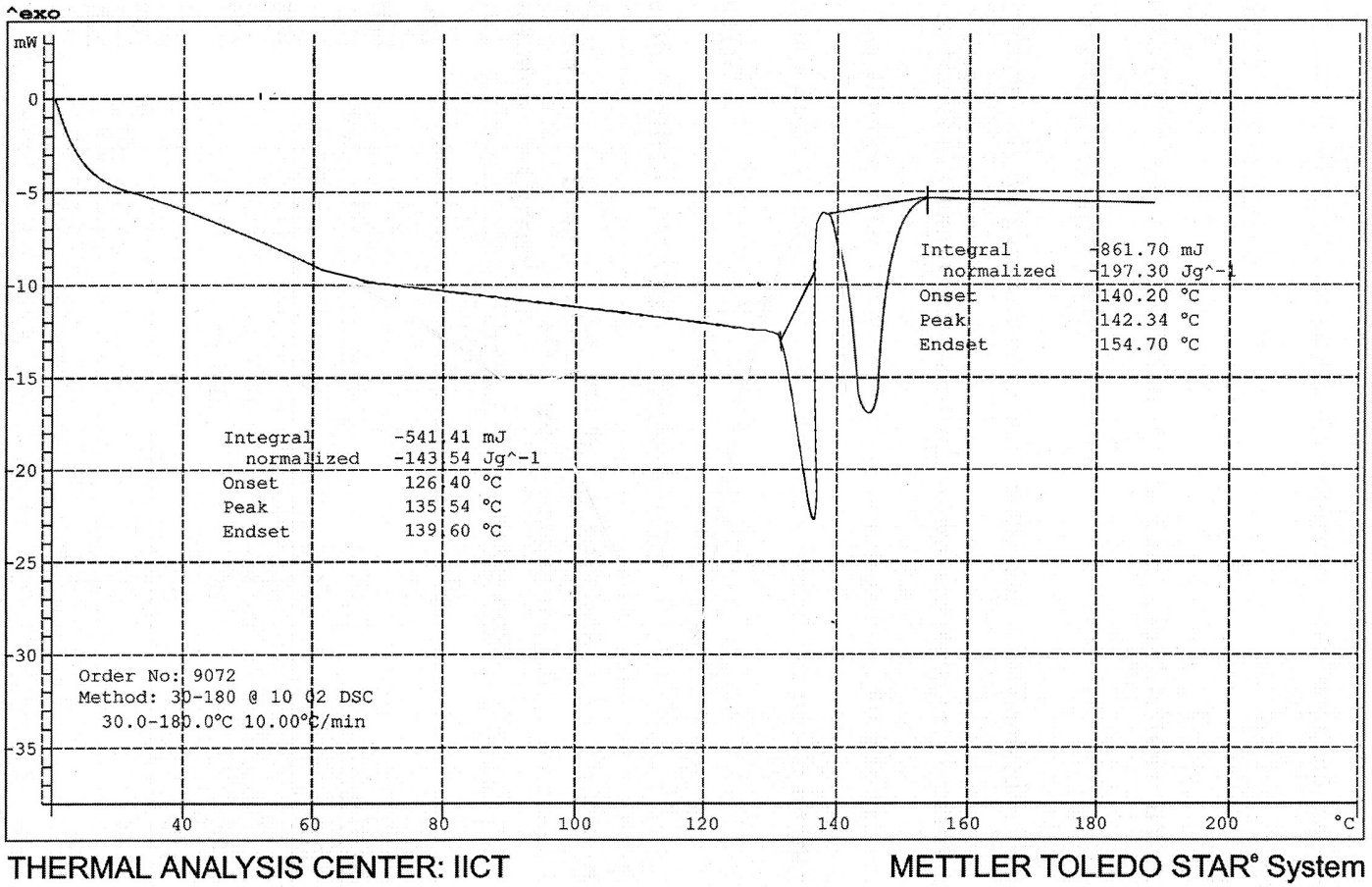


Figure 11: DSC thermogram of solid dispersion of aceclofenac with PVP 40 (1:9) KM



Drug content uniformity

The prepared aceclofenac solid dispersion was tested for drug content uniformity. From each batch of solid dispersion prepared in different ratios, equivalent to 100mg of aceclofenac solid dispersion were taken and analyzed for drug content uniformity.

Estimation of aceclofenac in solid dispersion by UV Spectroscopy:

Accurately weighed amount of solid dispersion was dissolved in 100 ml of pH 7.4 phosphate buffer in 100ml volumetric flask which was previously clean and dry. This solution after suitable dilution was measured for absorbance at 273 nm in a Jasco V530 UV visible spectrophotometer. The results were shown in table.11, 12.

Table.11 Drug content uniformity in solid dispersions (Kneading method)

Solid dispersion	Drug : carrier	Amount of SD taken	Expected amount of aceclofenac in SD (mg)	Aceclofenac estimated by spectrophotometer (%)
Aceclofenac PVP10	1:1	200	100	96.3
	1:3	400	100	97.8
	1:9	1000	100	96.0
Aceclofenac PVP40	1:1	200	100	96.3
	1:3	400	100	93.6
	1:9	1000	100	96.3
Aceclofenac PVP360	1:1	200	100	99.0
	1:3	400	100	94.8
	1:9	1000	100	97.2
Aceclofenac PVP10 PVA8136	1:1	200	100	94.2
	1:3	400	100	99.0
	1:9	1000	100	97.2
Aceclofenac PVP 40 PVA8136	1:1	200	100	101.4
	1:3	400	100	100.2
	1:9	1000	100	99.6
Aceclofenac PVP360 PVA8136	1:1	200	100	101.4
	1:3	400	100	99.6
	1:9	1000	100	99.9

Table.12 Drug content uniformity in solid dispersions (Solvent evaporation method)

Solid dispersion	Drug : carrier	Amount of SD taken	Expected amount of aceclofenac in SD (mg)	Aceclofenac estimated by spectrophotometer (%)
Aceclofenac PVP10	1:1	200	100	94.5
	1:3	400	100	92.4
	1:9	1000	100	93.6
Aceclofenac PVP40	1:1	200	100	90.6
	1:3	400	100	94.5
	1:9	1000	100	95.4
Aceclofenac PVP360	1:1	200	100	99.3
	1:3	400	100	93.0
	1:9	1000	100	97.2
Aceclofenac PVP10 PVA8136	1:1	200	100	99.0
	1:3	400	100	92.4
	1:9	1000	100	100.2
Aceclofenac PVP140 PVA8136	1:1	200	100	94.5
	1:3	400	100	92.4
	1:9	1000	100	93.6
Aceclofenac PVP360 PVA8136	1:1	200	100	94.5
	1:3	400	100	96.3
	1:9	1000	100	97.8

Invitro dissolution studies:

The dissolution studies are the most important part of the evaluation of solid dispersion, where the dissolution of pure drug and solid dispersion is carried out. Dissolution rate studies of various solid dispersions were carried out in phosphate buffer of PH 7.4 using USP XXII dissolution apparatus (Electro lab).

Dissolution method:

900ml of phosphate buffer of PH 7.4 was used as dissolution medium. SDs equivalent to 100mg of aceclofenac was taken in a hard gelatin capsule; a stainless steel wire was wound around the capsule to sink. The paddle type stirrer was adjusted to 75 rpm. The temperature was maintained at 37°±2℃. 5 ml aliquot

dissolution media was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution medium. The samples were analyzed for aceclofenac after suitable dilution by measuring the absorption values at 273 nm using Jasco V 530 UV visible spectrophotometer. Phosphate buffer of pH 7.4 used as a blank. The percentage of aceclofenac dissolved at various time intervals was calculated and plotted against time. T_{50}, T_{90} values were calculated from these dissolution curves. The results are shown in table.13-24 and fig. 13-24.

Figure: 12 Dissolution apparatus (Electrolab)

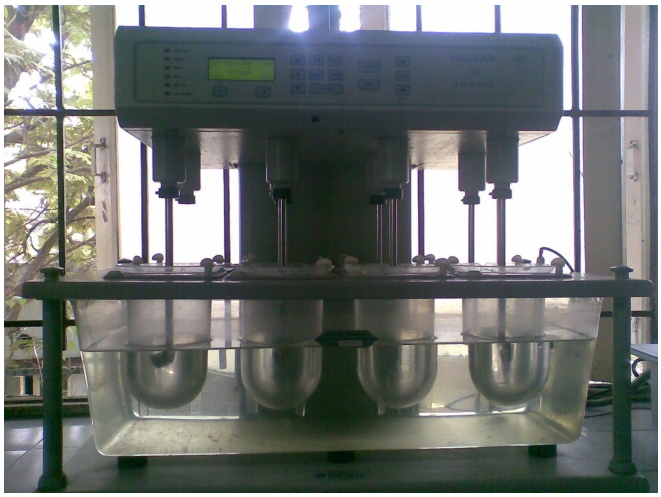


Table.13 Dissolutiion profile of aceclofenac from PVP 10 solid dispersion at different drug carreir ratios (kneading method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	18.9	17.55	35.1
30	4.5	10.35	54.9	45.9	45.0
45	10.2	22.5	70.2	56.7	54.9
60	15.75	36.0	73.3	63.0	54.9
75	21.6	48.6	76.5	72.0	63.0
90	23.4	54.9	76.5	72.0	82.8
105	24.2	62.1	77.4	73.35	91.8
120	25.4	62.1	77.4	73.35	91.8

Figure 13 Dissolutiion profile of aceclofenac from PVP 10 solid dispersion at different drug carreir ratios (kneading method)

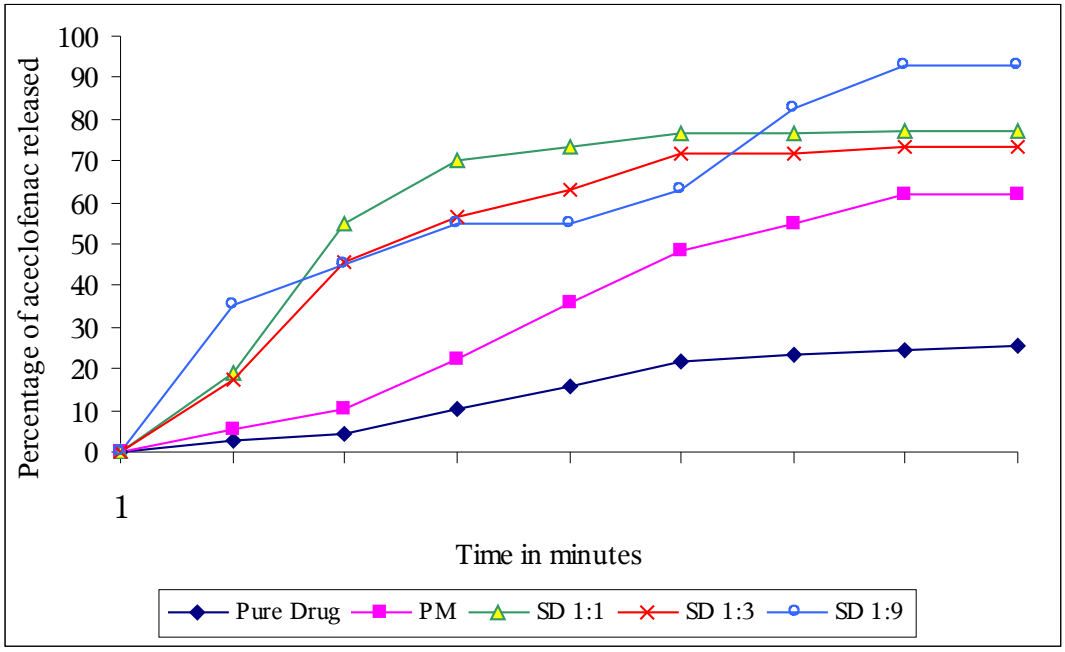


Table.14 Dissolution profile of aceclofenac from PVP 40 solid dispersion at different drug carrier ratios (kneading method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	20.7	9.0	20.7
30	4.5	10.35	67.0	31.5	54.9
45	10.2	22.5	72.0	45.9	68.4
60	15.75	36.0	77.4	45.9	72.0
75	21.6	48.6	78.3	49.5	72.0
90	23.4	54.9	80.5	51.3	91.8
105	24.2	62.1	85.5	51.3	93.7
120	25.4	62.1	85.5	51.3	93.7

Figure 14 Dissolution profile of aceclofenac from PVP 40 solid dispersion at different drug carrier ratios (kneading method)

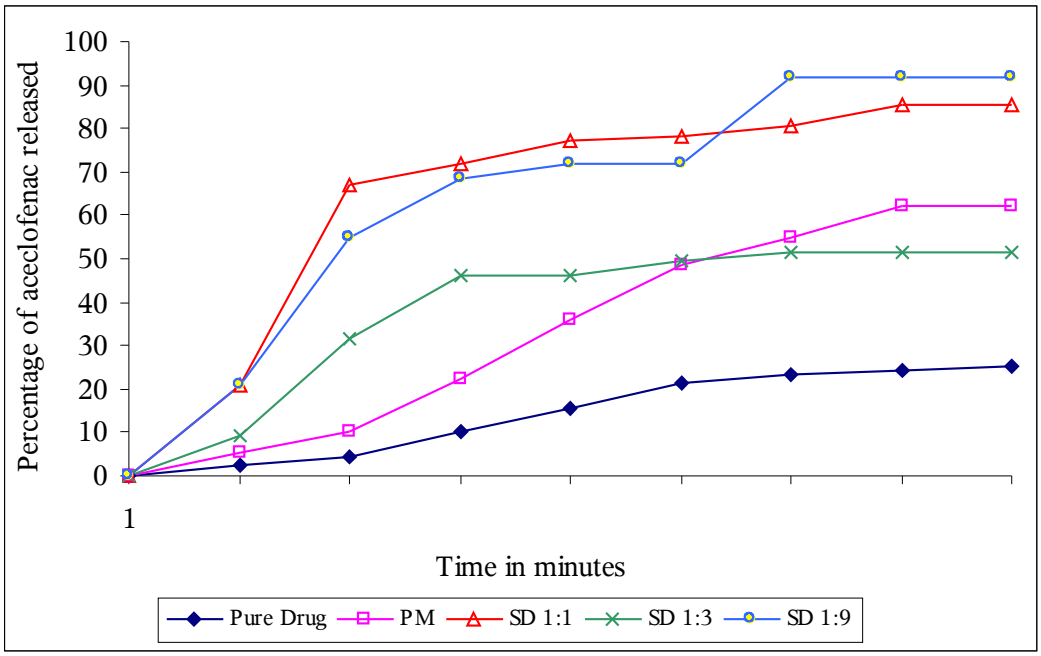


Table.15 Dissolution profile of aceclofenac from PVP 360 solid dispersion at different drug carrier ratios (kneading method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	20.7	18.9	1.8
30	4.5	10.35	54.9	53.1	10.8
45	10.2	22.5	68.4	63.9	52.2
60	15.75	36.0	72.0	68.4	52.2
75	21.6	48.6	72.0	68.4	68.4
90	23.4	54.9	91.8	70.2	68.4
105	24.2	62.1	91.8	70.2	82.8
120	25.4	62.1	91.8	72.0	95.4

Figure 15 Dissolution profile of aceclofenac from PVP 360 solid dispersion at different drug carrier ratios (kneading method)

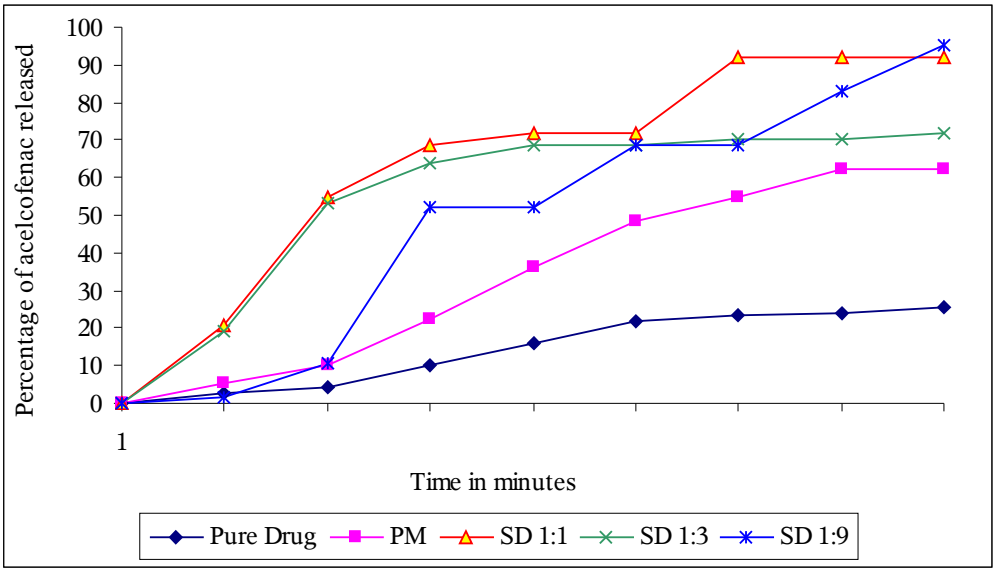


Table.16 Dissolution profile of aceclofenac from PVP 10; PVA 8136 solid dispersion at different drug carrier ratios (kneading method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	10.8	9.0	7.2
30	4.5	10.35	34.6	9.0	18.6
45	10.2	22.5	58.5	20.7	35.1
60	15.75	36.0	62.1	37.8	50.4
75	21.6	48.6	68.4	50.4	68.4
90	23.4	54.9	72.0	54.9	75.6
105	24.2	62.1	76.5	58.5	75.6
120	25.4	62.1	81.9	75.6	79.2

Figure 16 Dissolution profile of aceclofenac from PVP 10; PVA 8136 solid dispersion at different drug carrier ratios (kneading method)

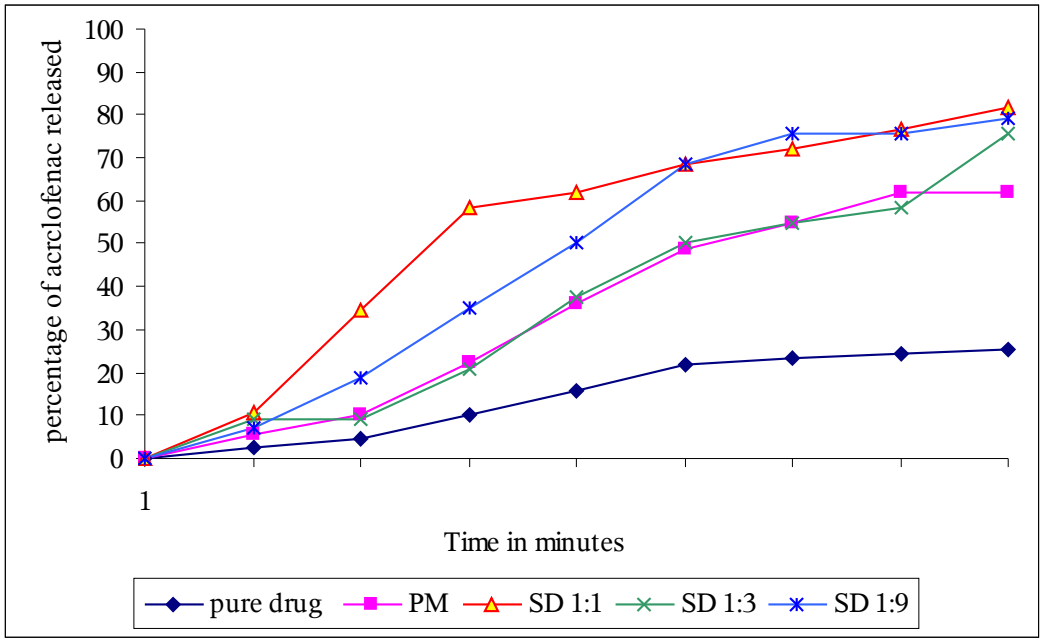


Table.17 Dissolution profile of aceclofenac from PVP 40; PVA 8136 solid dispersion at different drug carrier ratios (kneading method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	15.3	4.5	18.0
30	4.5	10.35	49.5	11.7	45.0
45	10.2	22.5	62.1	39.6	58.5
60	15.75	36.0	63.0	54.9	68.4
75	21.6	48.6	63.0	66.6	78.3
90	23.4	54.9	64.8	81.9	82.8
105	24.2	62.1	64.8	84.6	82.8
120	25.4	62.1	64.8	86.4	82.8

Figure 17 Dissolution profile of aceclofenac from PVP 40; PVA 8136 solid dispersion at different drug carrier ratios (kneading method)

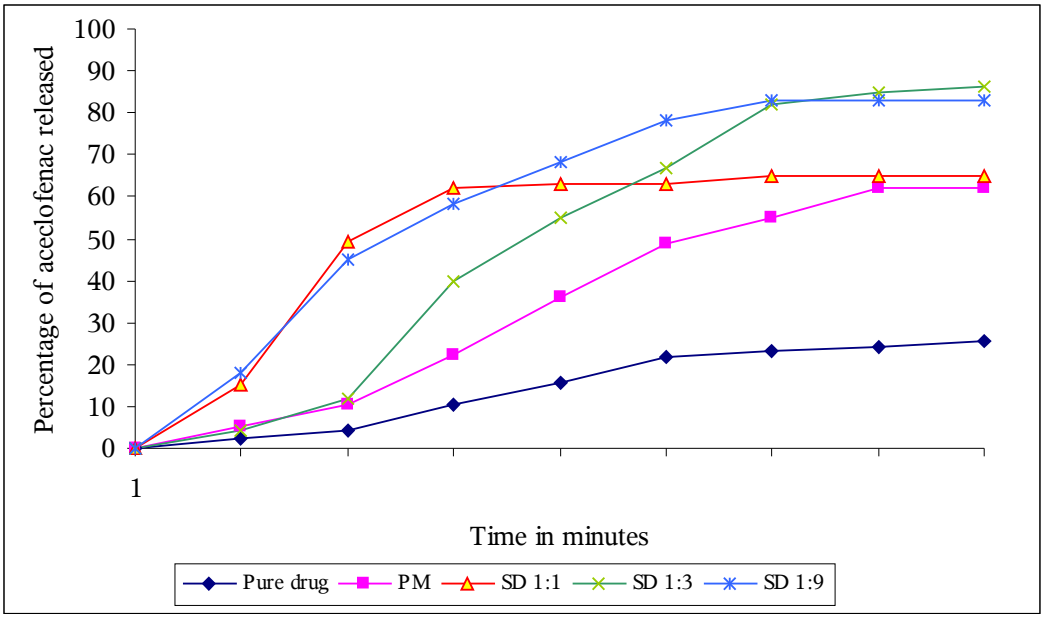


Table.18 Dissolution profile of aceclofenac from PVP 360; PVA 8136 solid dispersion at different drug carrier ratios (kneading method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	18.9	13.95	14.4
30	4.5	10.35	53.1	26.1	27.0
45	10.2	22.5	63.9	36.0	50.4
60	15.75	36.0	68.4	43.2	58.5
75	21.6	48.6	68.4	55.8	63.0
90	23.4	54.9	70.2	58.5	68.4
105	24.2	62.1	70.2	64.8	68.4
120	25.4	62.1	72.0	66.6	68.4

Figure 18 Dissolution profile of aceclofenac from PVP 360; PVA 8136 solid dispersion at different drug carrier ratios (kneading method)

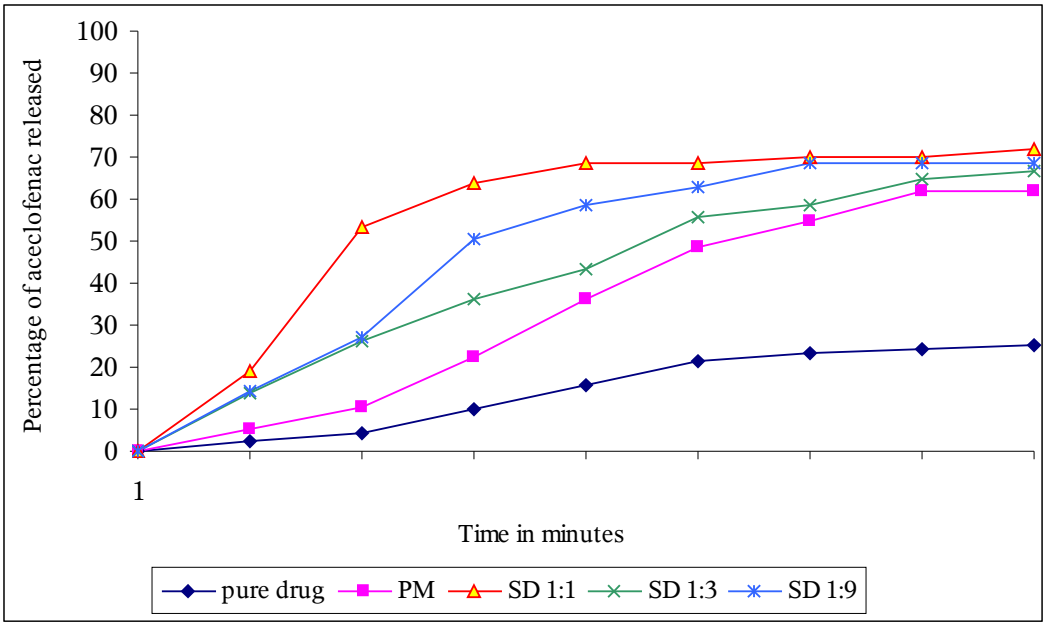


Table.19 Dissolution profile of aceclofenac from PVP 10 solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	16.2	7.2	25.2
30	4.5	10.35	45.9	13.9	56.7
45	10.2	22.5	55.8	49.5	63.9
60	15.75	36.0	65.7	56.7	70.2
75	21.6	48.6	66.6	62.1	73.3
90	23.4	54.9	67.5	62.1	73.3
105	24.2	62.1	68.4	64.8	75.6
120	25.4	62.1	76.45	67.0	75.6

Figure 19 Dissolution profile of aceclofenac from PVP 10 solid dispersion at different drug carrier ratios (solvent evaporation method)

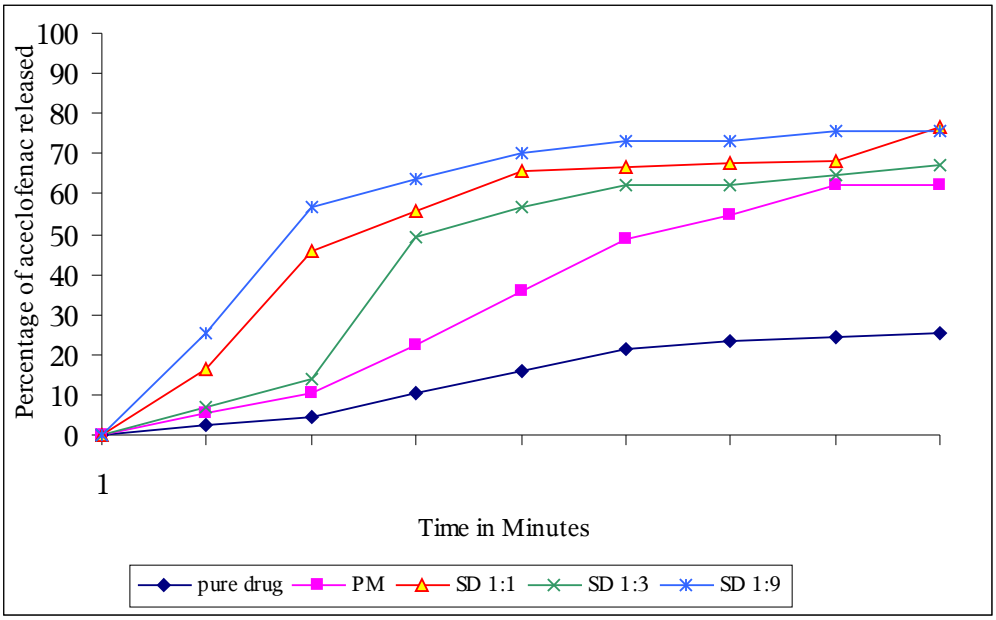


Table.20 Dissolution profile of aceclofenac from PVP 40 solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	7.2	5.85	18.0
30	4.5	10.35	14.4	17.55	31.5
45	10.2	22.5	33.3	22.5	37.8
60	15.75	36.0	46.3	63.0	52.2
75	21.6	48.6	56.7	67.95	54.9
90	23.4	54.9	61.2	67.95	54.9
105	24.2	62.1	65.7	71.1	58.5
120	25.4	62.1	67.5	71.1	58.5

Figure 20 Dissolution profile of aceclofenac from PVP 40 solid dispersion at different drug carrier ratios (solvent evaporation method)

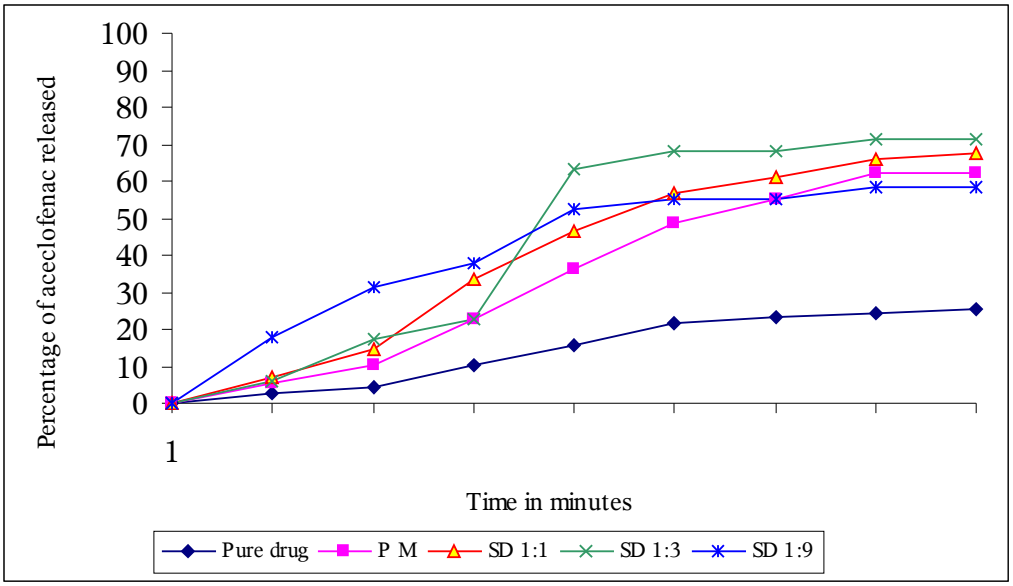


Table.21 Dissolution profile of aceclofenac from PVP 360 solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	13.5	5.85	3.6
30	4.5	10.35	53.1	29.25	18.0
45	10.2	22.5	61.65	40.95	18.0
60	15.75	36.0	70.2	53.1	35.0
75	21.6	48.6	75.6	62.1	45.0
90	23.4	54.9	79.2	64.8	45.0
105	24.2	62.1	81.0	66.6	50.4
120	25.4	62.1	81.9	71.1	57.6

Figure 21 Dissolution profile of aceclofenac from PVP 360 solid dispersion at different drug carrier ratios (solvent evaporation method)

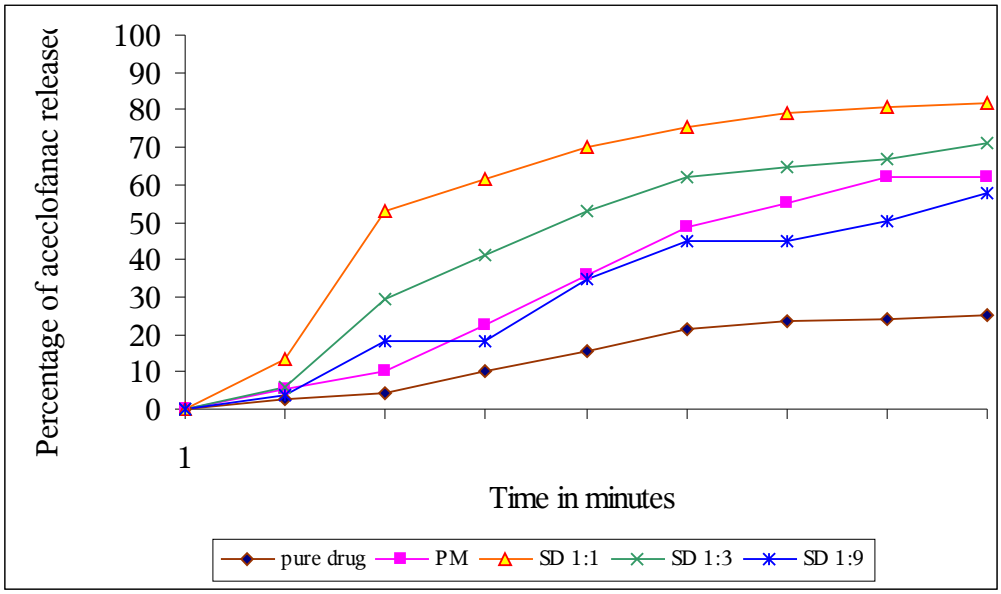


Table.22 Dissolution profile of aceclofenac from PVP 10; pva8136 solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	12.6	12.6	10.8
30	4.5	10.35	33.5	29.2	14.4
45	10.2	22.5	41.4	49.5	27.9
60	15.75	36.0	58.5	58.5	45.0
75	21.6	48.6	61.2	64.8	63.0
90	23.4	54.9	67.5	68.4	68.4
105	24.2	62.1	68.4	68.4	75.6
120	25.4	62.1	72.0	70.2	75.6

Figure 22 Dissolution profile of aceclofenac from PVP 10; PVA8136 solid dispersion at different drug carrier ratios (solvent evaporation method)

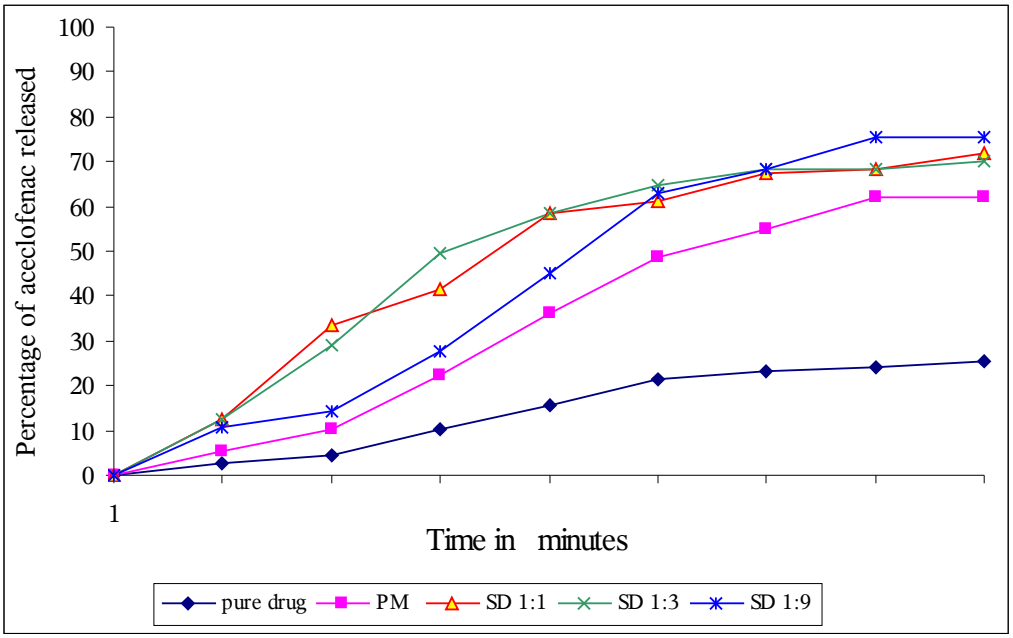


Table.23 Dissolution profile of aceclofenac from PVP 40; PVA8136 solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	7.2	1.8	9.0
30	4.5	10.35	26.1	5.4	9.0
45	10.2	22.5	41.4	13.95	20.7
60	15.75	36.0	47.7	26.1	37.8
75	21.6	48.6	54.9	32.4	50.4
90	23.4	54.9	58.5	36.6	54.9
105	24.2	62.1	64.8	43.2	58.5
120	25.4	62.1	64.8	45.0	75.6

Figure 23 Dissolution profile of aceclofenac from PVP 40; PVA8136 solid dispersion at different drug carrier ratios (solvent evaporation method)

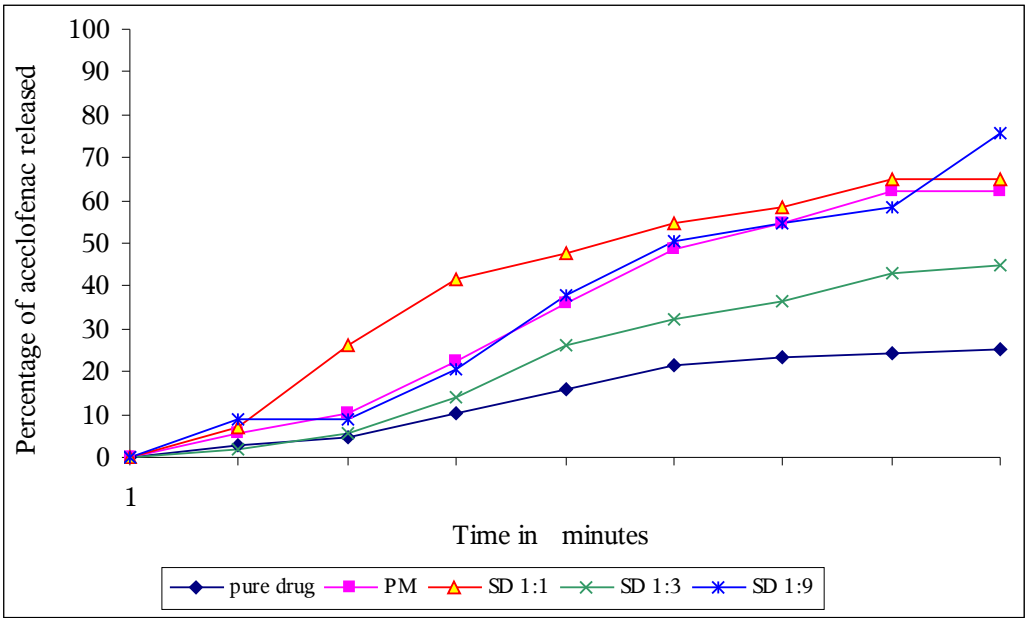


Table.24 Dissolution profile of aceclofenac from PVP 360; PVA8136 solid dispersion at different drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage release of aceclofenac from different drug carrier ratios				
	Pure drug 100 mg	Physical mixture	1:1	1:3	1:9
0	0	0	0	0	0
15	2.6	5.4	17.55	7.2	7.2
30	4.5	10.35	34.2	10.8	14.4
45	10.2	22.5	49.5	26.1	28.8
60	15.75	36.0	54.9	26.1	36.0
75	21.6	48.6	56.7	34.2	43.2
90	23.4	54.9	59.4	34.2	43.2
105	24.2	62.1	68.4	41.4	55.8
120	25.4	62.1	68.4	47.7	63.0

Figure 24 Dissolution profile of aceclofenac from PVP 360; PVA8136 solid dispersion at different drug carrier ratios (solvent evaporation method)

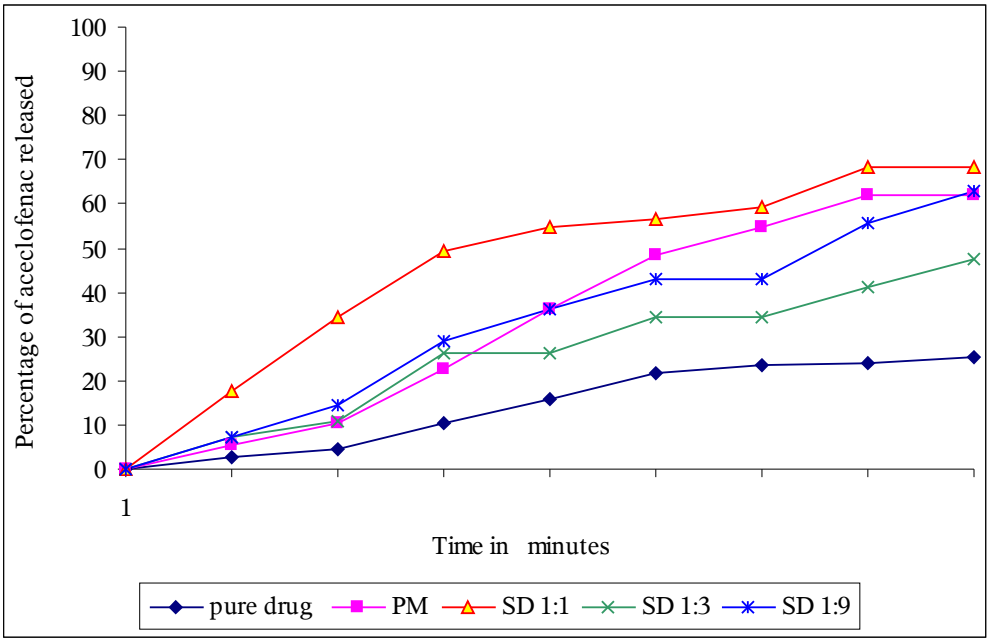


Table.25 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:1 ratio. (kneading method)

Time in minutes	Percentage release of aceclofenac from						
	Pure drug 100 mg	PVP 10	PVP 40	PVP 360	PVP 10; PVA 8136	PVP 40; PVA 8136	PVP 360; PVA 8136
0	0	0	0	0	0	0	0
15	2.6	18.9	20.7	20.7	10.8	15.3	17.55
30	4.5	54.9	67.0	54.9	34.6	49.5	34.2
45	10.2	70.2	72.0	68.4	58.5	62.1	49.5
60	15.75	73.3	77.4	72.0	62.1	63.0	54.9
75	21.6	76.5	78.3	72.0	68.4	63.0	56.7
90	23.4	76.5	80.5	91.8	72.0	64.8	59.4
105	24.2	77.4	85.5	91.8	76.5	64.8	68.4
120	25.4	77.4	85.5	91.8	81.9	64.8	68.4

Figure 28 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:1 ratio. (kneading method)

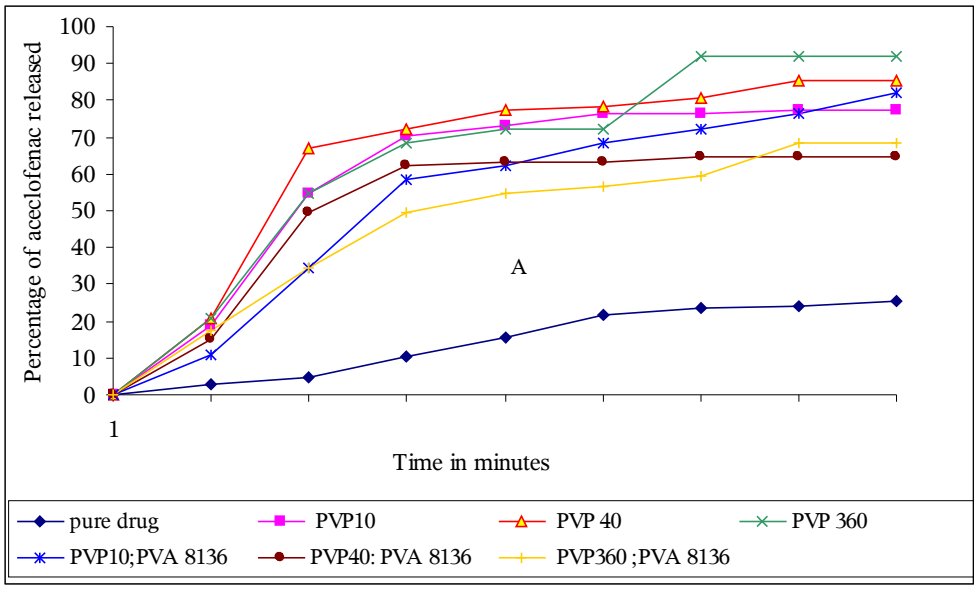


Table.26 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:3 ratio. (kneading method)

Time in minutes	Percentage release of aceclofenac from						
	Pure drug 100 mg	PVP 10	PVP 40	PVP 360	PVP10; PVA8136	PVP 40; PVA8136	PVP 360; PVA8136
0	0	0	0	0	0	0	0
15	2.6	17.55	9.0	18.9	9.0	4.5	13.95
30	4.5	45.9	31.5	53.1	9.0	11.7	26.1
45	10.2	56.7	45.9	63.9	20.7	39.6	36.0
60	15.75	63.0	45.9	68.4	37.8	54.9	43.2
75	21.6	72.0	49.5	68.4	50.4	66.6	55.8
90	23.4	72.0	51.3	70.2	54.9	81.9	58.5
105	24.2	73.35	51.3	70.2	58.5	84.6	64.8
120	25.4	73.35	51.3	72.0	75.6	86.4	66.6

Figure 26 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:3 ratio. (kneading method)

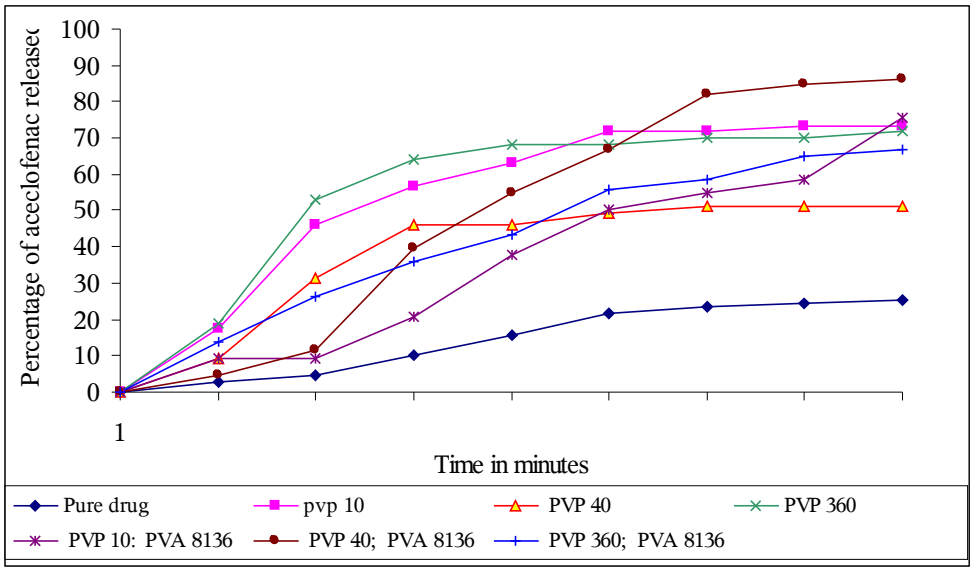


Table.27 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:9 ratio. (kneading method)

Time in minutes	Percentage release of aceclofenac from						
	Pure drug 100 mg	PVP 10	PVP 40	PVP 360	PVP10; PVA8136	PVP 40; PVA8136	PVP360; PVA8136
0	0	0	0	0	0	0	0
15	2.6	35.1	20.7	1.8	7.2	18.0	14.4
30	4.5	45.0	54.9	10.8	18.6	45.0	27.0
45	10.2	54.9	68.4	52.2	35.1	58.5	50.4
60	15.75	54.9	72.0	52.2	50.4	68.4	58.5
75	21.6	63.0	72.0	68.4	68.4	78.3	63.0
90	23.4	82.8	91.8	68.4	75.6	82.8	68.4
105	24.2	92.7	93.7	82.8	75.6	82.8	68.4
120	25.4	92.7	93.7	95.4	79.2	82.8	68.4

Figure 27 Table.27 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:9 ratio. (kneading method)

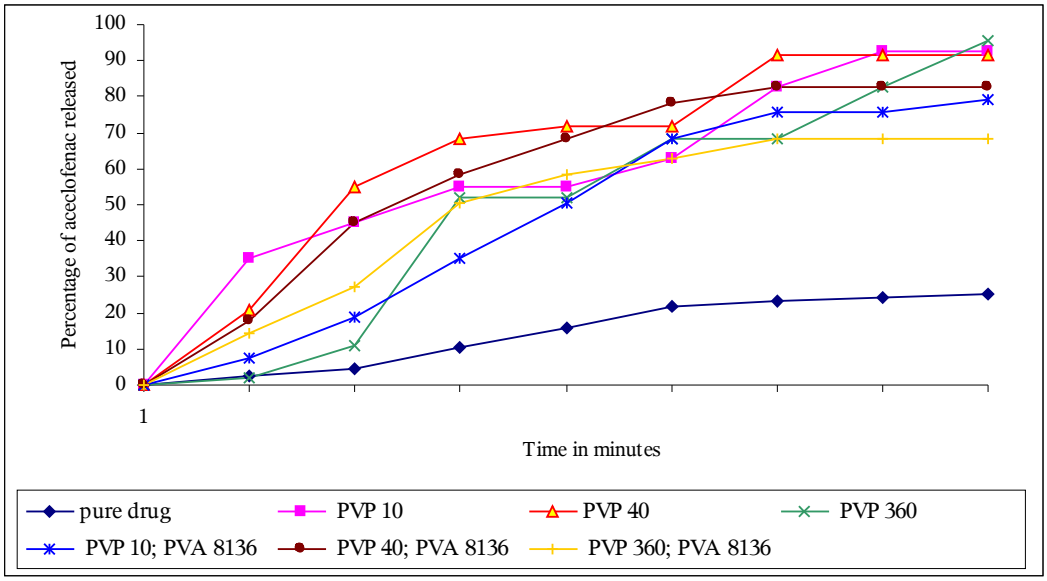


Table.28 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:1 ratio. (solvent evaporation method)

Time In Minutes	Percentage release of aceclofenac from						
	Pure drug 100 mg	SD with PVP 10	SD with PVP 40	SD with PVP 360	SD with PVP 10; PVA 8136	SD with PVP 40; PVA 8136	SD with PVP 360; PVA 8136
0	0	0	0	0	0	0	0
15	2.6	16.2	7.2	13.5	12.6	7.2	17.55
30	4.5	45.9	14.4	53.1	33.5	26.1	34.2
45	10.2	55.8	33.3	61.65	41.4	41.4	49.5
60	15.75	65.7	46.3	70.2	58.5	47.7	54.9
75	21.6	66.6	56.7	75.6	61.2	54.9	56.7
90	23.4	67.5	61.2	79.2	67.5	58.5	59.4
105	24.2	68.4	65.7	81.0	68.4	64.8	68.4
120	25.4	76.45	67.5	81.9	72.0	64.8	68.4

Figure 28 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:1 ratio. (solvent evaporation method)

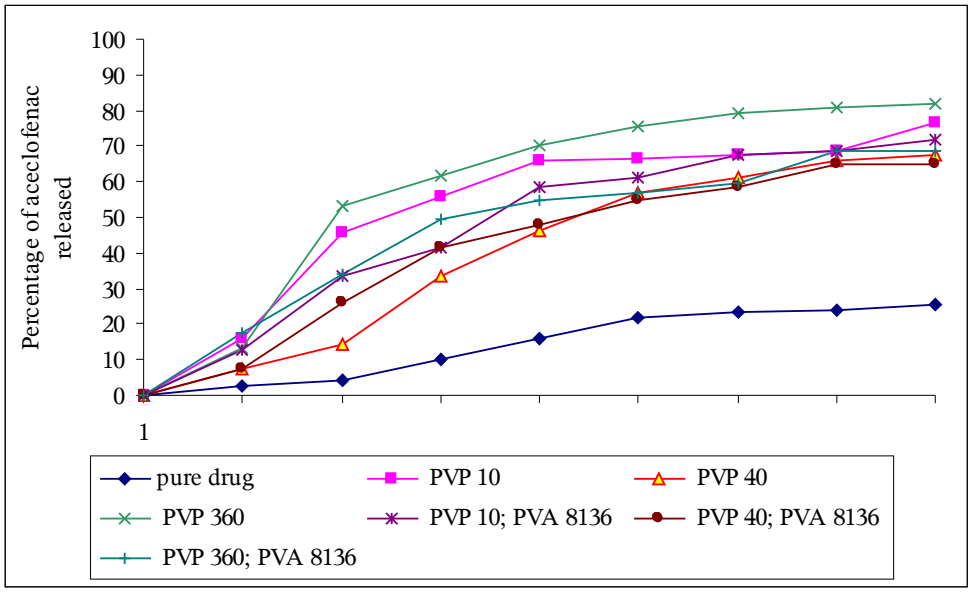


Table.29 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:3 ratio. (solvent evaporation method)

Time In Minutes	Percentage release of aceclofenac from						
	Pure drug 100 mg	SD with PVP 10	SD with PVP 40	SD with PVP 360	SD with PVP 10; PVA 8136	SD with PVP 40; PVA 8136	SD with PVP 360; PVA 8136
0	0	0	0	0	0	0	0
15	2.6	7.2	7.2	5.85	12.6	1.8	7.2
30	4.5	13.9	13.9	29.25	29.2	5.4	10.8
45	10.2	49.5	49.5	40.95	49.5	13.95	26.1
60	15.75	56.7	56.7	53.1	58.5	26.1	26.1
75	21.6	62.1	62.1	62.1	64.8	32.4	34.2
90	23.4	62.1	62.1	64.8	68.4	36.6	34.2
105	24.2	64.8	64.8	66.6	68.4	43.2	41.4
120	25.4	67.0	67.0	71.1	70.2	45.0	47.7

Figure 29 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:3 ratio. (solvent evaporation method)

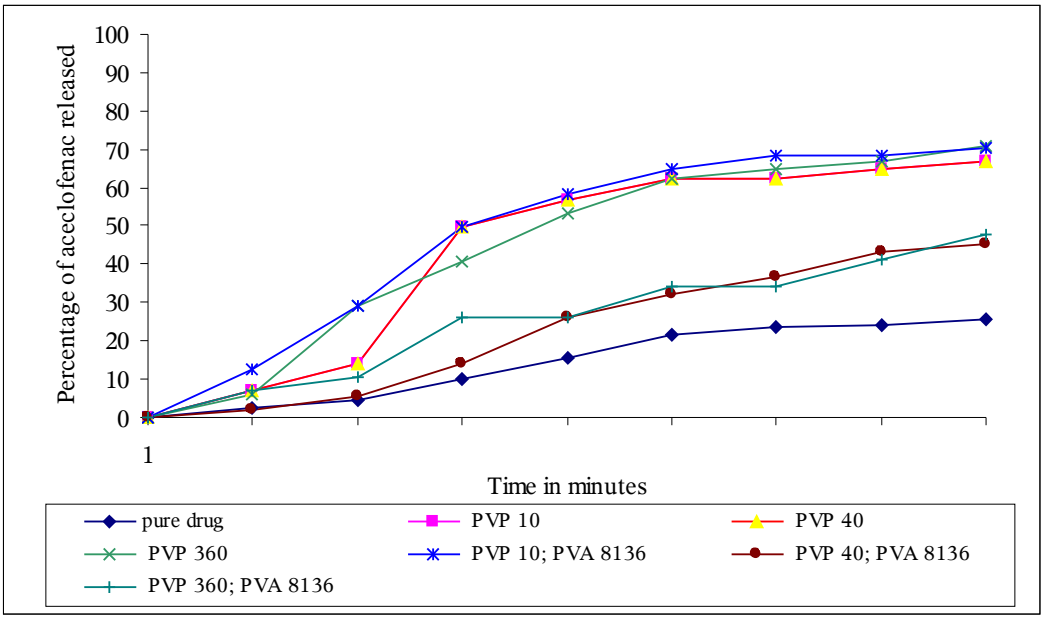


Table.30 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:9 ratio. (solvent evaporation method)

Time in minutes	Percentage release of aceclofenac from						
	Pure drug 100 mg	SD with PVP 10	SD with PVP 40	SD with PVP 360	SD with PVP 10; PVA 8136	SD with PVP 40; PVA 8136	SD with PVP 360; PVA 8136
0	0	0	0	0	0	0	0
15	2.6	25.2	18.0	3.6	10.8	9.0	7.2
30	4.5	56.7	31.5	18.0	14.4	9.0	14.4
45	10.2	63.9	37.8	18.0	27.9	20.7	28.8
60	15.75	70.2	52..2	35.0	45.0	37.8	36.0
75	21.6	73.3	54.9	45.0	63.0	50.4	43.2
90	23.4	73.3	54.9	45.0	68.4	54.9	43.2
105	24.2	75.6	58.5	50.4	75.6	58.5	55.8
120	25.4	75.6	58.5	57.6	75.6	75.6	63.0

Figure 30 Dissolution profile of aceclofenac pure form and from solid dispersions prepared with various carriers at 1:9 ratio. (solvent evaporation method)

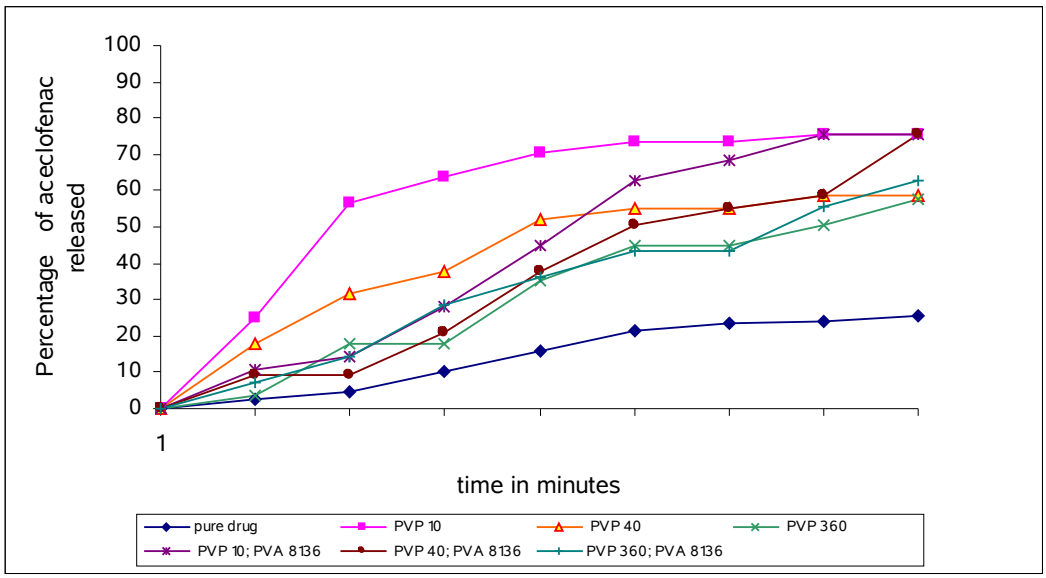


Table.31 Dissolution of aceclofenac pure form and from physical mixture with various carriers at drug: carrier ratio of 1:1

Time In Minutes	Percentage aceclofenac dissolved from						
	Pure drug 100 mg	PM with PVP 10	PM with PVP 40	PM with PVP 360	PM with PVP 10; PVA8136	PM with PVP 40; PVA8136	PM with PVP 360; PVA8136
0	0	0	0	0	0	0	0
15	2.6	5.4	10.35	9.0	9.0	5.4	10.35
30	4.5	10.35	18.9	9.0	17.55	15.75	24.3
45	10.2	22.5	31.5	31.5	34.2	27.45	34.42
60	15.75	36.0	39.6	34.2	36.0	37.8	37.8
75	21.6	48.6	51.3	43.2	43.2	45.9	39.6
90	23.4	54.9	53.1	51.3	46.35	46.35	40.95
105	24.2	62.1	53.1	53.1	48.6	48.6	48.6
120	25.4	62.1	53.1	53.1	49.5	49.5	48.6

Figure 31 Dissolution of aceclofenac pure form and from physical mixture with various carriers at drug: carrier ratio of 1:1

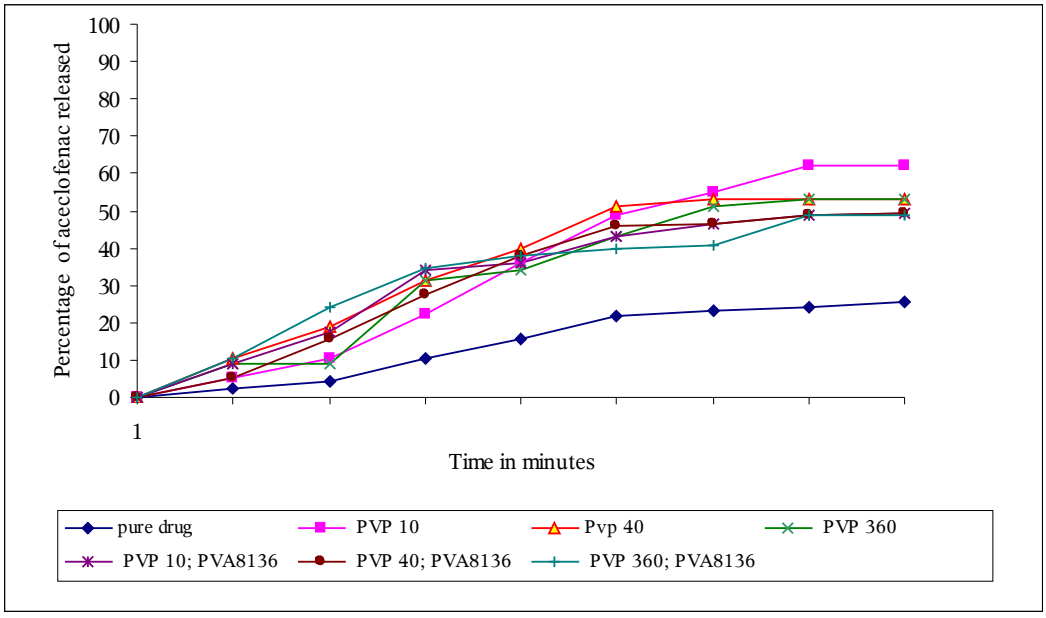


Table No.32 Percentage release of aceclofenac from various solid dispersions (kneading method)

Time in minutes	Percentage release of aceclofenac from																		
	Pure drug	ACE: PVP10			ACE: PVP40			ACE: PVP360			ACE: PVP10,PVA8136			ACE: PVP40,PVA8136			ACE: PVP360,PVA8136		
		1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	2.6	18.9	17.55	35.1	20.7	9.0	20.7	20.7	18.9	1.8	10.8	9.0	7.2	15.3	4.5	18.0	18.9	13.95	14.4
30	4.5	54.9	45.9	45.0	67.0	31.5	54.9	54.9	53.1	10.8	34.6	9.0	18.6	49.5	11.7	45.0	53.1	26.1	27.0
45	10.2	70.2	56.7	54.9	72.0	45.9	68.4	68.4	63.9	52.2	58.5	20.7	35.1	62.1	39.6	58.5	63.9	36.0	50.4
60	15.75	73.3	63.0	54.9	77.4	45.9	72.0	72.0	68.4	52.2	62.1	37.8	50.4	63.0	54.9	68.4	68.4	43.2	58.5
75	21.6	76.5	72.0	63.0	78.3	49.5	72.0	72.0	68.4	68.4	68.4	50.4	68.4	63.0	66.6	78.3	68.4	55.8	63.0
90	23.4	76.5	72.0	82.8	80.5	51.3	91.8	91.8	70.2	68.4	72.0	54.9	75.6	64.8	81.9	82.8	70.2	58.5	68.4

105	24.2	77.4	73.35	91.8	85.5	51.3	93.7	91.8	70.2	82.8	76.5	58.5	75.6	64.8	84.6	82.8	70.2	64.8	68.4
120	25.4	77.4	73.35	91.8	85.5	51.3	93.7	91.8	72.0	95.4	81.9	75.6	79.2	64.8	86.4	82.8	72.0	66.6	68.4

Table No.33 Percentage release of aceclofenac from various solid dispersions (solvent evaporation method)

Time in minutes	Percentage release of aceclofenac from																	
	Pure drug	ACE: PVP10			ACE: PVP40			ACE: PVP360			ACE: PVP10,PVA8136			ACE: PVP40,PVA8136			ACE: PVP360,PVA8136		
		1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	2.6	16.2	7.2	25.2	7.2	5.85	18.0	13.5	5.85	3.6	12.6	12.6	10.8	7.2	1.8	9.0	17.55	7.2	7.2
30	4.5	45.9	13.9	56.7	14.4	17.55	31.5	53.1	29.25	18.0	33.5	29.2	14.4	26.1	5.4	9.0	34.2	10.8	14.4
45	10.2	55.8	49.5	63.9	33.3	22.5	37.8	61.65	40.95	18.0	41.4	49.5	27.9	41.4	13.95	20.7	49.5	26.1	28.8
60	15.75	65.7	56.7	70.2	46.3	63.0	52..2	70.2	53.1	35.0	58.5	58.5	45.0	47.7	26.1	37.8	54.9	26.1	36.0
75	21.6	66.6	62.1	73.3	56.7	67.95	54.9	75.6	62.1	45.0	61.2	64.8	63.0	54.9	32.4	50.4	56.7	34.2	43.2
90	23.4	67.5	62.	73.	61.	67.9	54.9	79.2	64.8	45.	67.5	68.4	68.4	58.	36.6	54.	59.4	34.2	43.2

			1	3	2	5				0				5		9			
105	24.2	68.4	64. 8	75. 6	65. 7	71.1	58.5	81.0	66.6	50. 4	68.4	68.4	75.6	64. 8	43.2	58. 5	68.4	41.4	55.8
120	25.4	76.4 5	67. 0	75. 6	67. 5	71.1	58.5	81.9	71.1	57. 6	72.0	70.2	75.6	64. 8	45.0	75. 6	68.4	47.7	63.0

Table.34 Relation between % carrier and T_{50}, T_{90} values for aceclofenac- PVP10 solid dispersions:

% of drug	%of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	27.5	40.5	-	-
1	3	40.0	53.0	-	-
1	9	40.0	26.5	102.0	-

Table.35 Relation between % carrier and T_{50}, T_{90} values for aceclofenac- PVP 40 solid dispersions:

% of drug	%of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	22.5	66.0	-	-
1	3	88.0	47.5	-	-
1	9	27.5	57.5	88.5	-

Table.36 Relation between % carrier and T_{50}, T_{90} values for aceclofenac- PVP 360 solid dispersions:

% of drug	%of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	27.5	28.5	88.5	-
1	3	28.5	56.5	-	-
1	9	43.0	104.0	113.5	-

Table.37 Relation between % carrier and T_{50}, T_{90} values for aceclofenac- PVP10, PVA8136 solid dispersions

% of drug	%of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	38.5	51.5	-	-
1	3	74.5	51.5	-	-
1	9	59.5	59.5	-	-

Table.38 Relation between % carrier and T_{50}, T_{90} values for aceclofenac- PVP 40, PVA 8136 solid dispersions

% of drug	%of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	36.5	68.5	-	-
1	3	54.5	-	-	-
1	9	38.5	74.5	-	-

Table.39 Relation between % carrier and T_{50}, T_{90} values for aceclofenac- PVP 360, PVA 8136 solid dispersions

% of drug	%of carrier	T_{50} (min)		T_{90} (min)	
		KM	SE	KM	SE
1	1	28.0	54.6	-	-
1	3	67.0	-	-	-
1	9	44.5	94.0	-	-

Table.40 Percentage aceclofenac undissolved from pure form and from PVP 10 solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	94.6 (1.975)	81.1 (1.909)	82.45 (1.916)	64.9 (1.812)
30	95.5 (1.980)	89.65 (1.952)	45.1 (1.650)	54.1 (1.733)	55.0 (1.740)
45	89.8 (1.953)	77.5 (1.889)	29.8 (1.474)	43.3 (1.636)	45.1 (1.654)
60	84.25 (1.925)	64.0 (1.806)	26.7 (1.426)	37.0 (1.568)	45.1 (1.654)
75	78.4 (1.894)	51.4 (1.710)	23.5 (1.371)	28.0 (1.447)	37.0 (1.568)
90	76.6 (1.884)	45.1 (1.654)	23.5 (1.371)	28.0 (1.447)	17.2 (1.235)
105	75.8 (1.879)	37.9 (1.578)	22.6 (1.354)	26.65 (1.425)	7.3 (0.863)
120	74.6 (1.872)	37.9 (1.578)	22.6 (1.354)	26.65 (1.425)	7.3 (0.863)

Figure 32 Percentage aceclofenac undissolved from pure form and from PVP 10 solid dispersions at various drug carrier ratios (kneading method)

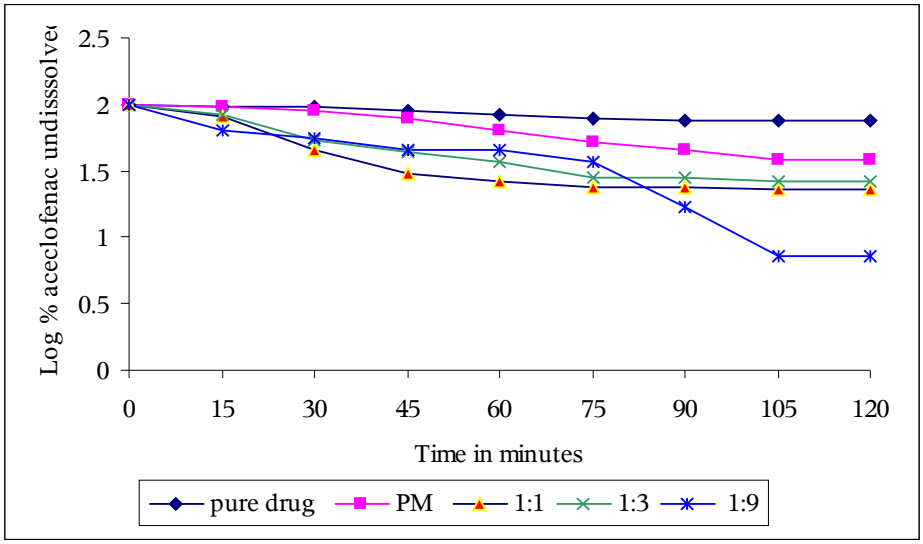


Table.41 Percentage aceclofenac undissolved from pure form and from PVP 40 solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	89.65 (1.952)	79.3 (1.899)	87.4 (1.941)	79.3 (1.899)
30	95.5 (1.980)	81.1 (1.909)	33.0 (1.518)	65.8 (1.818)	45.1 (1.654)
45	89.8 (1.953)	68.5 (1.855)	28.0 (1.447)	48.7 (1.687)	31.6 (1.499)
60	84.25 (1.925)	60.4 (1.781)	22.6 (1.354)	43.3 (1.636)	28.0 (1.447)
75	78.4 (1.894)	48.7 (1.687)	21.7 (1.336)	31.6 (1.499)	28.0 (1.447)
90	76.6 (1.884)	46.9 (1.671)	19.5 (1.290)	29.8 (1.474)	8.2 (0.913)
105	75.8 (1.879)	46.9 (1.671)	14.5 (1.161)	29.8 (1.474)	8.2 (0.913)
120	74.6 (1.872)	46.9 (1.671)	14.5 (1.161)	28.0 (1.447)	8.2 (0.913)

Figure 33 Percentage aceclofenac undissolved from pure form and from PVP 40 solid dispersions at various drug carrier ratios (kneading method)

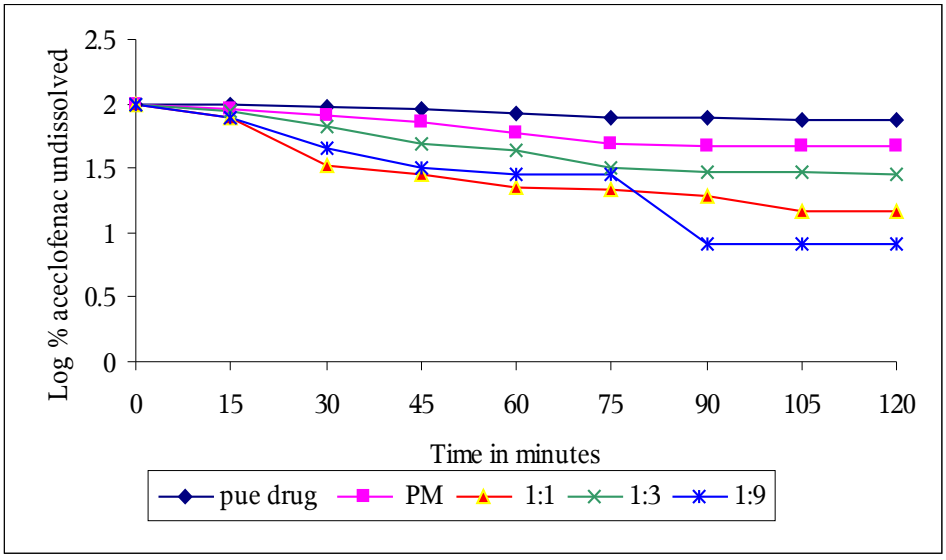


Table.42 Percentage aceclofenac undissolved from pure form and from PVP 360 solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	91.0 (1.959)	79.3 (1.899)	81.1 (1.909)	98.2 (1.992)
30	95.5 (1.980)	91.0 (1.959)	45.1 (1.654)	46.9 (1.671)	89.2 (1.952)
45	89.8 (1.953)	68.5 (1.835)	31.6 (1.449)	36.1 (1.557)	47.8 (1.679)
60	84.25 (1.925)	65.8 (1.818)	28.0 (1.447)	31.6 (1.499)	47.8 (1.679)
75	78.4 (1.894)	56.8 (1.754)	28.0 (1.447)	31.6 (1.499)	31.6 (1.499)
90	76.6 (1.884)	48.7 (1.687)	8.2 (0.913)	29.8 (1.474)	31.6 (1.499)
105	75.8 (1.879)	46.9 (1.671)	8.2 (0.913)	29.8 (1.474)	17.2 (1.235)
120	74.6 (1.872)	46.9 (1.671)	8.2 (0.913)	28.0 (1.447)	4.6 (0.662)

Figure 34 Percentage aceclofenac undissolved from pure form and from PVP 360 solid dispersions at various drug carrier ratios (kneading method)

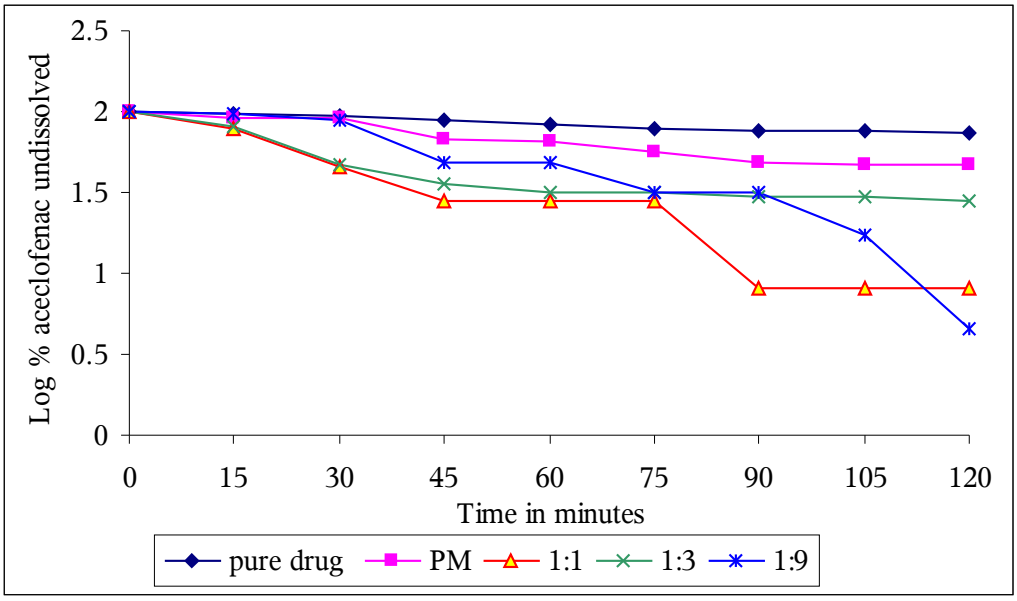


Table.43 Percentage aceclofenac undissolved from pure form and from PVP 10: PVA 8136 solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	91.0 (1.959)	89.2 (1.950)	91.0 (1.959)	92.8 (1.967)
30	95.5 (1.980)	82.45 (1.916)	65.4 (1.815)	91.0 (1.959)	81.4 (1.910)
45	89.8 (1.953)	65.8 (1.818)	41.5 (1.618)	79.3 (1.899)	64.9 (1.812)
60	84.25 (1.925)	64.0 (1.806)	37.9 (1.578)	62.2 (1.793)	49.6 (1.695)
75	78.4 (1.894)	56.8 (1.754)	31.6 (1.499)	49.6 (1.695)	31.6 (1.499)
90	76.6 (1.884)	53.65 (1.729)	28.0 (1.447)	45.1 (1.654)	24.4 (1.387)
105	75.8 (1.879)	51.4 (1.710)	23.5 (1.371)	41.5 (1.618)	24.4 (1.387)
120	74.6 (1.872)	50.5 (1.703)	18.1 (1.257)	24.4 (1.387)	20.8 (1.318)

Figure 35 Percentage aceclofenac undissolved from pure form and from PVP 10: PVA 8136 solid dispersions at various drug carrier ratios (kneading method)

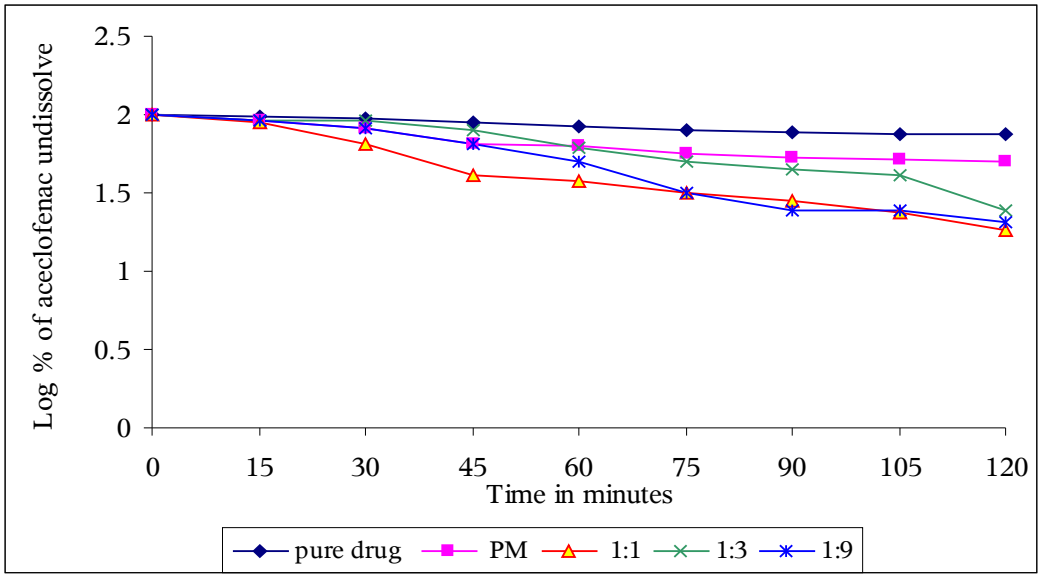


Table.44 Percentage aceclofenac undissolved from pure form and from PVP 40: PVA 8136 solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	94.6 (1.975)	84.7 (1.927)	95.5 (1.980)	82.0 (1.913)
30	95.5 (1.980)	84.25 (1.925)	50.5 (1.703)	88.3 (1.945)	55.0 (1.740)
45	89.8 (1.953)	72.55 (1.860)	37.9 (1.578)	60.4 (1.781)	41.5 (1.618)
60	84.25 (1.925)	62.2 (1.793)	37.0 (1.568)	45.1 (1.654)	31.6. (1.499)
75	78.4 (1.894)	54.1 (1.733)	37.0 (1.568)	33.4 (1.523)	21.7 (1.337)
90	76.6 (1.884)	53.65 (1.729)	35.2 (1.546)	18.1 (1.257)	17.2 (1.235)
105	75.8 (1.879)	51.4 (1.710)	35.2 (1.546)	15.4 (1.187)	17.2 (1.235)
120	74.6 (1.872)	50.5 (1.703)	35.2 (1.546)	13.6 (1.133)	17.2 (1.235)

Figure 36 Percentage aceclofenac undissolved from pure form and from PVP 40: PVA 8136 solid dispersions at various drug carrier ratios (kneading method)

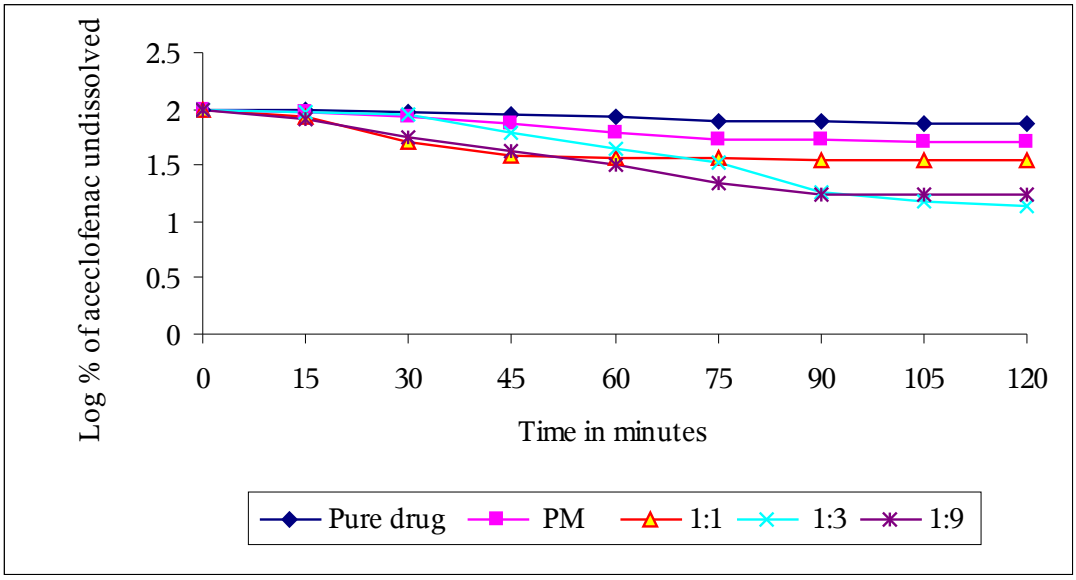


Table.45 Percentage aceclofenac undissolved from pure form and from PVP 360: PVA 8136 solid dispersions at various drug carrier ratios (kneading method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	89.65 (1.952)	81.1 (1.909)	86.05 (1.934)	85.6 (1.932)
30	95.5 (1.980)	75.7 (1.879)	46.9 (1.671)	73.9 (1.818)	73.0 (1.863)
45	89.8 (1.953)	65.58 (1.816)	36.1 (1.557)	64.0 (1.806)	49.6 (1.695)
60	84.25 (1.925)	62.2 (1.793)	31.6 (1.499)	56.8 (1.754)	41.5 (1.618)
75	78.4 (1.894)	60.4 (1.781)	31.6 (1.499)	44.2 (1.645)	37.0 (1.568)
90	76.6 (1.884)	59.65 (1.771)	29.8 (1.474)	41.5 (1.618)	31.6 (1.499)
105	75.8 (1.879)	51.4 (1.710)	29.8 (1.474)	35.2 (1.546)	31.6 (1.499)
120	74.6 (1.872)	51.4 (1.710)	28.0 (1.447)	33.4 (1.523)	31.6 (1.499)

Figure 37 Percentage aceclofenac undissolved from pure form and from PVP 360: PVA 8136 solid dispersions at various drug carrier ratios (kneading method)

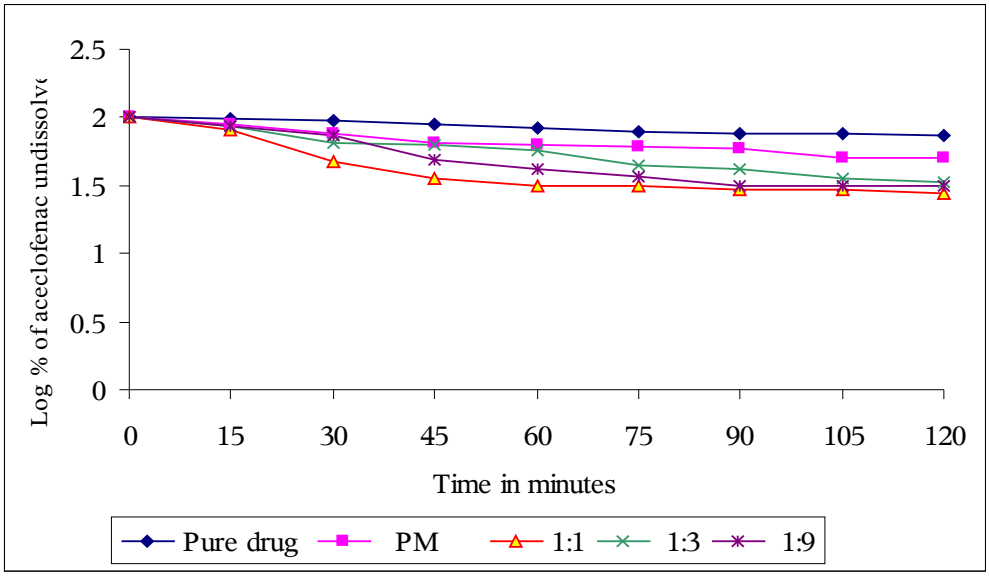


Table.46 Percentage aceclofenac undissolved from pure form and from PVP 10 solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	94.6 (1.975)	83.8 (1.923)	92.8 (1.967)	74.8 (1.873)
30	95.5 (1.980)	89.65 (1.952)	54.1 (1.733)	86.1 (1.935)	43.3 (1.636)
45	89.8 (1.953)	77.5 (1.889)	44.2 (1.645)	50.5 (1.703)	36.1 (1.557)
60	84.25 (1.925)	64.0 (1.806)	34.3 (1.535)	43.3 (1.636)	29.8 (1.474)
75	78.4 (1.894)	51.4 (1.710)	33.4 (1.523)	37.9 (1.578)	26.7 (1.426)
90	76.6 (1.884)	45.1 (1.654)	32.5 (1.511)	37.9 (1.578)	26.7 (1.426)
105	75.8 (1.879)	37.9 (1.578)	31.5 (1.498)	35.2 (1.546)	24.4 (1.387)
120	74.6 (1.872)	37.9 (1.578)	23.5 (1.371)	33.0 (1.518)	24.4 (1.387)

Figure 38 Percentage aceclofenac undissolved from pure form and from PVP 10 solid dispersions at various drug carrier ratios (solvent evaporation method)

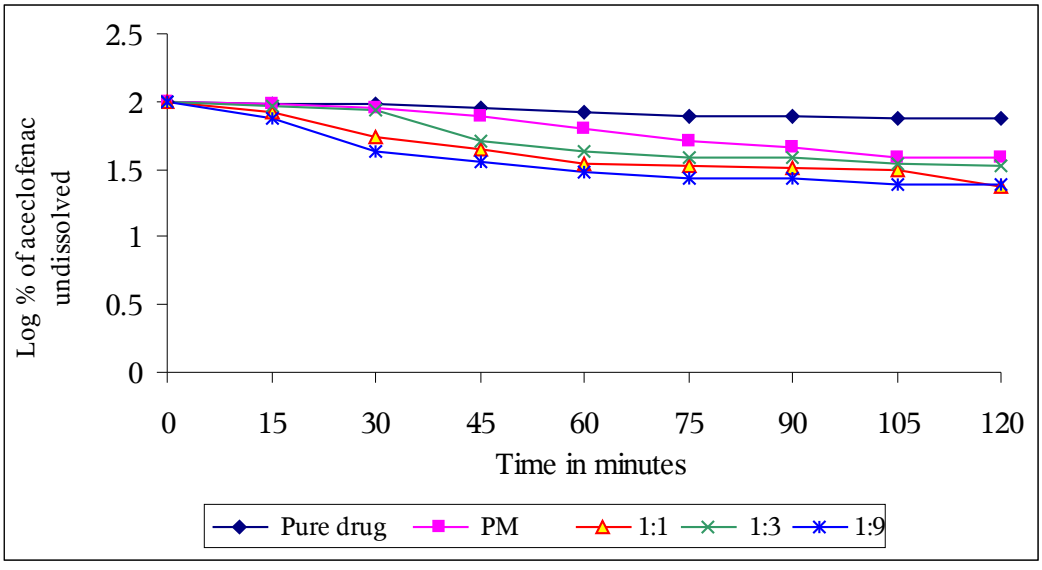


Table.47 Percentage aceclofenac undissolved from pure form and from PVP 40 solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	89.65 (1.952)	92.8 (1.967)	94.15 (1.973)	82.0 (1.913)
30	95.5 (1.980)	81.1 (1.909)	85.6 (1.932)	82.45 (1.916)	68.5 (1.835)
45	89.8 (1.953)	68.5 (1.855)	66.7 (1.824)	77.5 (1.889)	62.2 (1.793)
60	84.25 (1.925)	60.4 (1.781)	53.7 (1.729)	37.0 (1.568)	47.8 (1.679)
75	78.4 (1.894)	48.7 (1.687)	43.3 (1.636)	32.05 (1.505)	45.1 (1.654)
90	76.6 (1.884)	46.9 (1.671)	38.8 (1.588)	32.05 (1.505)	45.1 (1.654)
105	75.8 (1.879)	46.9 (1.671)	34.3 (1.535)	28.9 (1.460)	41.5 (1.618)
120	74.6 (1.872)	46.9 (1.671)	32.5 (1.511)	28.9 (1.460)	41.5 (1.618)

Figure 39 Percentage aceclofenac undissolved from pure form and from PVP 40 solid dispersions at various drug carrier ratios (solvent evaporation method)

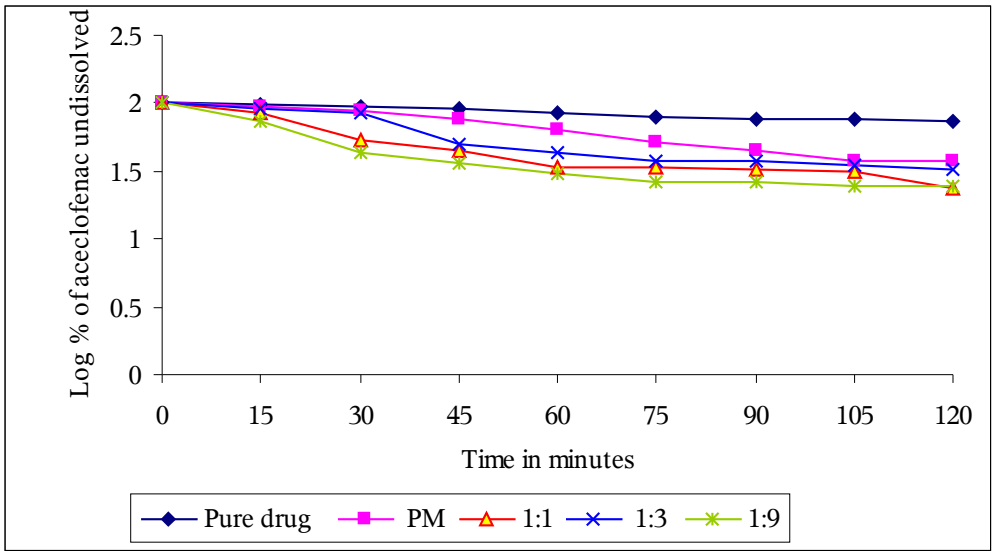


Table.48 Percentage aceclofenac undissolved from pure form and from PVP 360 solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	0	0	0	0	0
15	97.4 (1.988)	91.0 (1.959)	86.5 (1.937)	94.15 (1.973)	96.4 (1.984)
30	95.5 (1.980)	91.0 (1.959)	46.9 (1.671)	70.75 (1.849)	82.0 (1.913)
45	89.8 (1.953)	68.5 (1.835)	38.35 (1.583)	59.05 (1.771)	82.0 (1.913)
60	84.25 (1.925)	65.8 (1.818)	29.8 (1.474)	46.9 (1.671)	65.0 (1.812)
75	78.4 (1.894)	56.8 (1.754)	24.4 (1.387)	37.9 (1.578)	55.0 (1.740)
90	76.6 (1.884)	48.7 (1.687)	20.8 (1.318)	35.2 (1.546)	55.0 (1.740)
105	75.8 (1.879)	46.9 (1.671)	19.0 (1.278)	33.4 (1.523)	49.6 (1.695)
120	74.6 (1.872)	46.9 (1.671)	18.1 (1.257)	28.9 (1.460)	42.4 (1.627)

Figure 40 Percentage aceclofenac undissolved from pure form and from PVP 360 solid dispersions at various drug carrier ratios (solvent evaporation method)

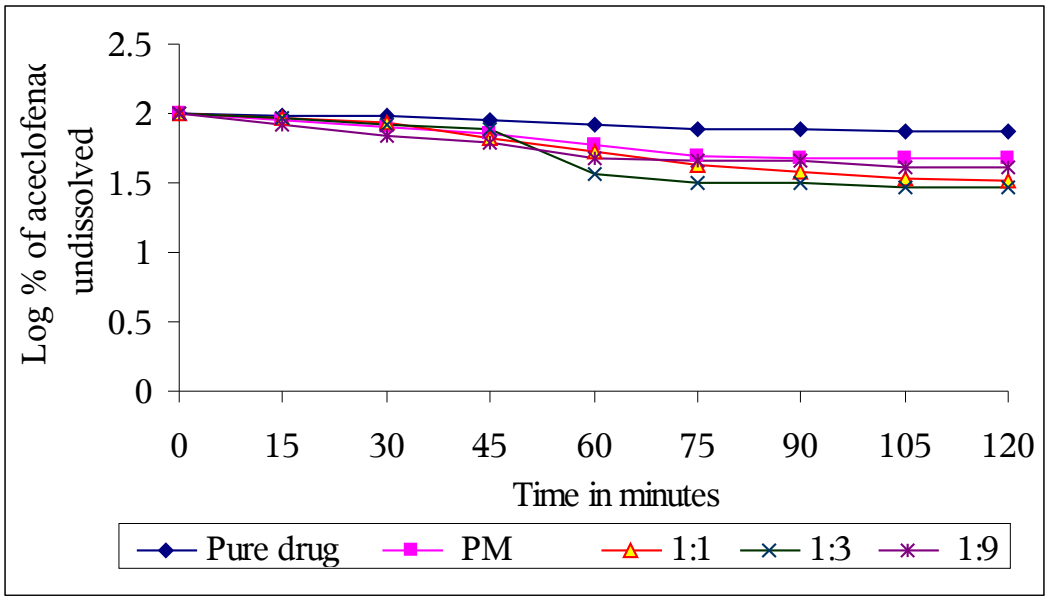


Table.49 Percentage aceclofenac undissolved from pure form and from PVP 10: PVA 8136 solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	91.0 (1.959)	87.4 (1.941)	87.4 (1.941)	89.2 (1.950)
30	95.5 (1.980)	82.45 (1.916)	66.5 (1.822)	70.8 (1.850)	85.6 (1.932)
45	89.8 (1.953)	65.8 (1.818)	58.6 (1.767)	50.5 (1.703)	72.1 (1.857)
60	84.25 (1.925)	64.0 (1.806)	41.5 (1.618)	41.5 (1.618)	55.0 (1.740)
75	78.4 (1.894)	56.8 (1.754)	38.8 (1.588)	35.2 (1.546)	37.0 (1.568)
90	76.6 (1.884)	53.65 (1.729)	32.5 (1.511)	31.6 (1.499)	31.6 (1.499)
105	75.8 (1.879)	51.4 (1.710)	31.6 (1.499)	31.6 (1.499)	24.4 (1.387)
120	74.6 (1.872)	50.5 (1.703)	28.0 (1.447)	29.8 (1.474)	24.4 (1.387)

Figure41 Percentage aceclofenac undissolved from pure form and from PVP 10: PVA 8136 solid dispersions at various drug carrier ratios (solvent evaporation method)

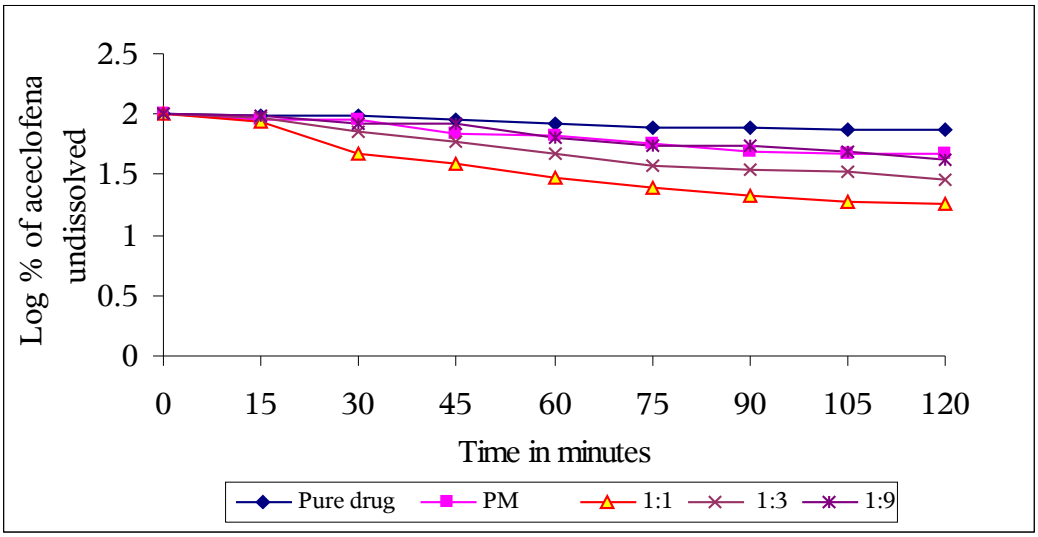


Table.50 Percentage aceclofenac undissolved from pure form and from PVP 40: PVA 8136 solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	94.6 (1.975)	92.8 (1.967)	98.2 (1.992)	91.0 (1.959)
30	95.5 (1.980)	84.25 (1.925)	73.9 (1.868)	94.6 (1.975)	91.0 (1.959)
45	89.8 (1.953)	72.55 (1.860)	58.6 (1.767)	86.05 (1.934)	79.0 (1.899)
60	84.25 (1.925)	62.2 (1.793)	52.3 (1.718)	73.9 (1.868)	62.2 (1.793)
75	78.4 (1.894)	54.1 (1.733)	45.1 (1.654)	67.6 (1.829)	49.6 (1.695)
90	76.6 (1.884)	53.65 (1.729)	41.5 (1.618)	63.4 (1.802)	45.1 (1.654)
105	75.8 (1.879)	51.4 (1.710)	35.2 (1.546)	56.8 (1.754)	41.5 (1.618)
120	74.6 (1.872)	50.5 (1.703)	35.2 (1.546)	55.0 (1.740)	24.4 (1.387)

Figure42 Percentage aceclofenac undissolved from pure form and from PVP 40: PVA 8136 solid dispersions at various drug carrier ratios (solvent evaporation method)

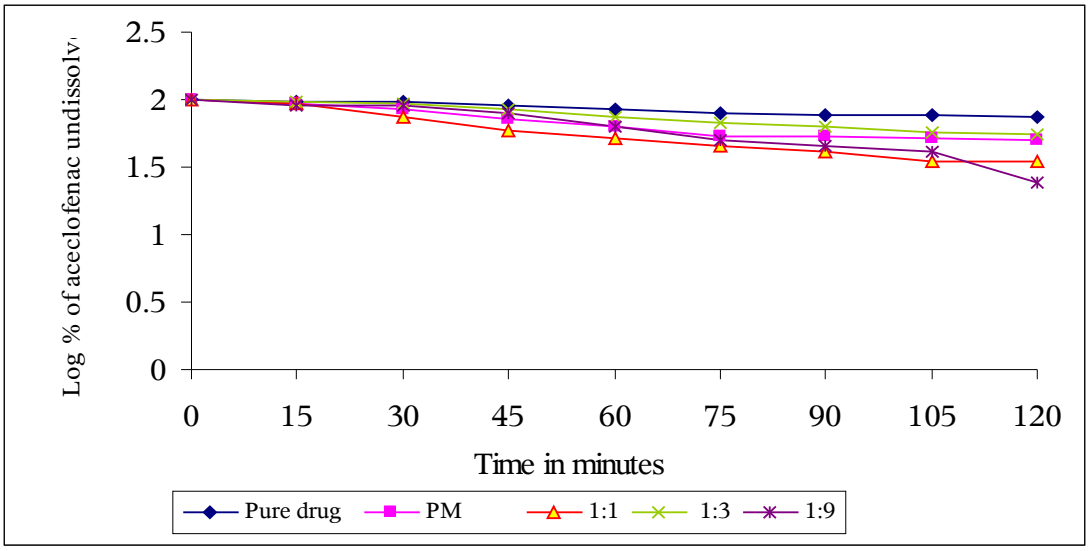


Table.51 Percentage aceclofenac undissolved from pure form and from PVP 360: PVA 8136 solid dispersions at various drug carrier ratios (solvent evaporation method)

Time in minutes	Percentage aceclofenac undissolved from (log percentage aceclofenac undissolved)				
	Pure drug 100 mg	PM 1:1	1:1	1:3	1:9
0	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)	100 (2.0)
15	97.4 (1.988)	89.65 (1.952)	82.45 (1.916)	92.8 (1.967)	92.8 (1.967)
30	95.5 (1.980)	75.7 (1.879)	65.8 (1.818)	89.2 (1.950)	85.6 (1.932)
45	89.8 (1.953)	65.58 (1.816)	50.5 (1.703)	73.9 (1.868)	71.2 (1.852)
60	84.25 (1.925)	62.2 (1.793)	45.1 (1.654)	73.9 (1.868)	64.0 (1.806)
75	78.4 (1.894)	60.4 (1.781)	43.3 (1.636)	65.8 (1.818)	56.8 (1.754)
90	76.6 (1.884)	59.65 (1.771)	40.6 (1.608)	65.8 (1.818)	56.8 (1.754)
105	75.8 (1.879)	51.4 (1.710)	31.6 (1.499)	58.6 (1.767)	44.2 (1.645)
120	74.6 (1.872)	51.4 (1.710)	31.6 (1.499)	52.3 (1.718)	37.0 (1.568tit)

Figure 43 Percentage aceclofenac undissolved from pure form and from PVP 360: PVA 8136 solid dispersions at various drug carrier ratios (solvent evaporation method)

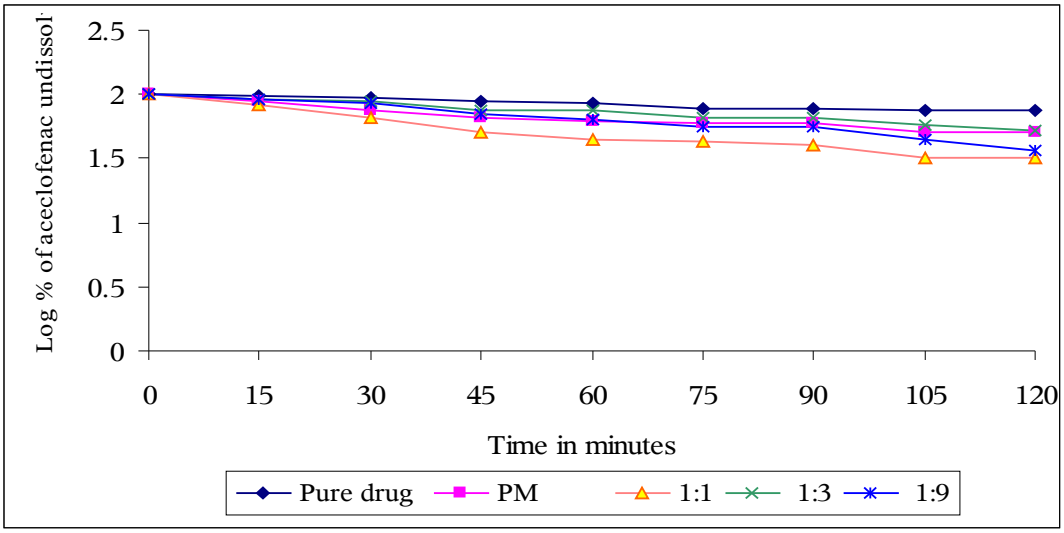


Table.52 First order rate constant for aceclofenac dissolution from various solid dispersions

Sample	K (min^{-1})	
	KM	SE
Pure drug	0.002149	
PM	0.003560	
ACE: PVP 10		
1:1	0.00198	0.00176
1:3	0.00256	0.00201
1:9	0.00312	0.00299
ACE: PVP 40		
1:1	0.02971	0.02561
1:3	0.04286	0.0486
1:9	0.05460	0.0500
ACE: PVP 360		
1:1	0.0346	0.02986
1:3	0.04201	0.0486
1:9	0.0501	0.0520
ACE: PVP 10, PVA 8136		
1:1	0.00616	0.0046
1:3	0.00677	0.00561
1:9	0.005757	0.00617
ACE: PVP 40, PVA 8136		
1:1	0.0040	0.00365
1:3	0.00307	0.00402
1:9	0.00523	0.00468
ACE: PVP 360, PVA 8136		
1:1	0.00405	0.002351
1:3	0.00616	0.00623
1:9	0.00677	0.00587

RESULTS AND DISCUSSION

Solid dispersion of aceclofenac were prepared by depositing on the polymers namely PVP10, PVP40, PVP360 and PVA 8136 by solvent evaporation method and kneading method. Solid dispersions at drug: carrier ratios (1:1, 1:3, 1:9) were prepared and summarized in table no.8 all solid dispersions prepared were found to be fine and free flowing powders. The percent of drug content in the solid dispersions were given in table .11, 12. there was no significant loss of drug during the preparation of solid dispersions and the proportion of drug and carrier remained the same as that initially taken. The estimated drug content of the prepared solid dispersions was in the range of 100±8%.

The prepare solid dispersions were characterized by TLC, FTIR, X-ray diffraction and Differential Scanning Calorimetry

Thin Layer Chromatography

In TLC studies, aceclofenac dispersed in various carriers showed the same Rf value as pure compound and no additional spots were detected. TLC studies thus indicated no interaction between aceclofenac and carriers in the solid dispersions prepared. This observation also indicated that aceclofenac was not decomposed during the preparation of solid dispersions.

FT-IR Spectral Analysis

Compatibility studies of aceclofenac and the carriers PVP and PVA were carried out by using FT-IR. The IR spectra obtained are given in fig.3-5. In aceclofenac IR spectrum, intense peaks were noticed at 2935.13 cm^{-1} (–CH_2 stretching), 2717.21 cm^{-1} (–OH stretching), 1718.26 cm^{-1} (–C=O stretching), 1585.2 cm^{-1} (aro.ring stretching) and 1348 cm^{-1} (–NH stretching).

IR spectra of aceclofenac and its solid dispersions are identical. The principal IR absorption peaks of aceclofenac were all observed in the spectra of aceclofenac as well as its dispersions. IR spectra indicated no interaction between aceclofenac and carriers in the solid dispersions.

Powder X- Ray Diffraction

X-ray diffraction studies indicated the presence of celecoxib in amorphous form in solid dispersion fig.8-9. Thus increased dissolution rate in the case of solid dispersions may be due to molecular dispersion of the drug in the amorphous form through the carriers.

Differential Scanning Calorimetry

The thermal behavior of aceclofenac-PVP 40 solid dispersion was studied using DSC to confirm the form formations of solid complexes are shown in fig.10-11. The DSC thermogram of exhibited an endothermic peak at 149ºC corresponding to its melting point, hence no polymorphs of aceclofenac could be found. For the solid dispersion system, this peak at 136ºC is very small; this result can be explained on the basis of major interaction between the polymer and aceclofenac. Furthermore the characteristic endothermic effect of PVP 40 is slightly shifted to lower temperature, indicating that aceclofenac has complexed with PVP 40. This phenomenon is indicative of stronger interaction between aceclofenac and PVP 40 in the solid state

Dissolution Studies

The dissolution profiles of pure drug, physical mixture and various solid dispersions were given in table .13-24 and fig. 13-24. The dissolution parameters of T_{50} and dissolution rate indicates rapid dissolution of aceclofenac from the solid dispersions when compared with the pure drug and physical mixture as the proportion of the polymer in the dispersion was increased the dissolution rate of aceclofenac also increased. T_{50} values were found to be decreased and K values found to be increased when the carrier concentration was raised indicating the fast dissolution of aceclofenac at higher carrier concentration. Among the solid dispersions prepared aceclofenac-PVP40 (1:9) dispersions gave the highest dissolution rate.

The order of dissolution of aceclofenac from various carriers is
PVP 360(KM)>PVP40 (KM)> PVP10 (KM)> PVP40, PVA 8136 (KM)> PVP10, PVA8136 (KM), PVP360 (SE)> PVP10 (SE)> PVP10, PVA 8136 (SE), PVP40, PVA 8136 (SE)> PVP360, PVA 8136 (KM)> PVP40 (SE)> PVP360, PVA 8136 (SE).

FORMULATION STUDIES ON SELECTED SOLID DISPERSION OF ACECLOFENAC

Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with or without suitable diluents, prepared by either compression or molding.

Advantages:

- They are unit dosage forms and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact of all oral dosage forms.
- They lend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral dosage forms.

Disadvantages:

- Some drugs resist compression into dense compact, owing to their flocculent, low density characters.
- Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or the tableting may require coating.
- Drugs with large dose may be difficult or impossible to formulate and manufacture as a tablet.

Formulation of tablets

Aceclofenac solid dispersion in PVP40 at a drug carrier ratio of 1:9 were formulated into tablets with usual additives and evaluated for drug release characteristics. Tablets containing 50 mg of aceclofenac were prepared using the solid dispersions and other additives as per the formula given in table 55.

Table.53 Formula of tablet formulation:

S.No	Ingredients	Formulations (mgs)	
		F1	F2
1	Aceclofenac	50	
2	Aceclofenac –PVP 40 (1:9) (KM)	-	500
3	Lactose	25	25
4	Micro crystalline cellulose	465	15
5	Talc	5	5
6	Magnesium stearate	5	5

Table.54 Materials used for tablet formulation:

Name of the materials	Name of company
Aceclofenac: PVP40 (1:9) drug carrier ratio.	-
Aceclofenac	Anglo French drugs and industries Pvt Limited
Lactose	SD Fine chemicals Ltd, Mumbai.
Micro crystalline cellulose	Loba chemie, Mumbai
Talc	Himedia Laboratories Pvt Ltd
Magnesium stearate	SD Fine chemicals Ltd, Mumbai.

Table.55 Equipments used for tablet formulation

Name of equipment	Name of company
Tablet punching machine	Rimek Mini Press 1
Tablet disintegration test apparatus	Remi equipments
Pfizer tablet hardness tester	Scientific engineering corporation
Roche friability tester	Remi equipments
Dissolution apparatus	Electoral TDT – 08L
UV spectrometer	Jasco V 530
pH testr 1 (water proof)	Oakton instruments.

Method

The required amount of drug and the other additives were mixed thoroughly in a mortar and the tablets are prepared by direct compression using Rimek Mini Press 1 punching machine. The prepared tablets were stored in screw capped glass bottles. The prepared tablets were evaluated for dissolution characteristics.

EVALUATION OF TABLETS: [51, 52.]

The formulated tablets were subjected for the following quality control tests.

- Weight variation
- Disintegration test
- Friability
- Hardness
- Drug content uniformity
- Dissolution

Weight variation test

Twenty tablets were taken weighed individually. They were evaluated for the weight variations. The weight variation allowed as IP limit is 5%. The weight of tablets with in the IP limits. The results were shown in table.56

Disintegration test

The USP device to test disintegration uses six glass tubes that are three inches long open at the top and held against 10 inch screen at the basket rack assembly. A tablet is placed in each tube and the basket is positioned in a 1 liter beaker of distilled water at 37±2°C, such that the tablets below the surface of the liquid on their movement and descend not closer than 2.5 cm from the bottom of the tester. The disintegration time is 4 min. 45 sec. The results were shown in table.56

Friability test

Friability test was performed on the formulated tablets. The weight of the tablets after undergoing 100 revolutions was found to be within the limits 0.5 to 1.0%. The results were shown in table.56

Hardness

Pfizer hardness tester was used for measuring the hardness of formulated aceclofenac SD tablets. Five tablets wee taken randomly and subjected to test. The hardness was found to be 4-5 kg/cm^2. The results were shown in table.56

Drug content uniformity

The prepared tablets containing aceclofenac solid dispersion was tested for drug content uniformity. Tablets were dissolved in 100 ml of pH 7.4 phosphate buffer in 100ml volumetric flask which was previously clean and dry. This solution after suitable dilution was measured for absorbance at 273 nm in a Jasco V530 UV visible spectrophotometer. The results were shown in table.56

Table 56

Weight variation, disintegrating time, friability, hardness and drug content uniformity of tablets containing solid dispersions of aceclofenac

S. No.	Weight variation(%),weight range of tablets(mg)	Disintegration time (sec)	Friability (%of loss of weight)	Hardness (kg/cm^2)	Drug content uniformity(%)
1	571-578	620-655	0.8	4.9	-
2	531	241	0.5	4.4	94.5
3	547	248	0.6	4.5	92.4
4	542	256	0.56	4.2	93.6
5	512	243	0.50	4.4	90.6
6	553	249	0.57	4.6	94.5
7	531	248	0.71	4.2	95.4
8	538	284	0.63	4.3	99.3
9	542	250	0.52	4.1	93.0
10	551	251	0.64	4.8	97.2
11	578	259	0.7	4.0	99.0
12	537	253	0.6	4.3	92.4
13	533	257	0.52	4.7	100.2
14	529	264	0.55	4.6	94.5
15	539	265	0.4	4.2	92.4
16	548	261	0.72	4.3	93.6
17	537	249	0.50	4.8	94.5
18	541	285	0.61	4.9	99.0
19	552	264	0.67	4.6	97.4
20	547	258	0.5	4.3	92.5

21	535	267	0.66	4.5	96.2

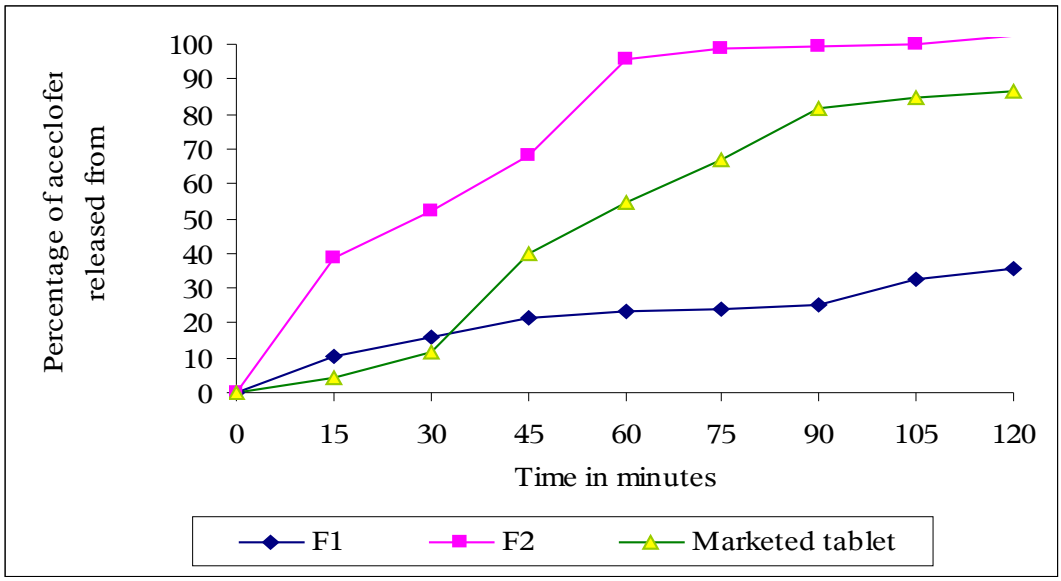
***In-vitro* Dissolution studies**

Dissolution of aceclofenac from various tablets was studied in USP dissolution medium. The tablets containing solid dispersions equivalent to 100mg of aceclofenac were taken and the paddle type stirrer was adjusted to 75 rpm. The temperature was maintained at 37±1°C. 5 ml aliquot dissolution media was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The samples were analyzed for aceclofenac by measuring absorbance at 273 nm using Jasco UV visible spectrometer. pH 7.4 phosphate buffer was used as blank. The percentage of aceclofenac dissolved at various time intervals was calculated and plotted against time. The results are shown in table 57. and fig.44.

Table No.57 Dissolution profile of aceclofenac from tablet formulation and from marketed tablets

Time in minutes	Percentage of aceclofenac released from		
	F1	F2	Marketed tablet
0	0	0	0
15	10.2	38.6	4.5
30	15.75	52.2	11.7
45	21.6	68.4	39.6
60	23.4	95.4	54.9
75	24.2	98.5	66.6
90	25.4	99.6	81.9
105	32.3	100.2	84.6
120	35.6	102.4	86.4

Figure 44 Dissolution profile of aceclofenac from tablet formulation and from marketed tablets



RESULTS AND DISCUSSION

The results of drug content, hardness, friability test, disintegration test, are given in subsequent chapters. All the batches fulfill the official IP requirements for tablets. Hardness of the tablets in all the batches was found to be 4 to 5 kg/cm^2 and was satisfactory. The percentage weight loss in the friability test was found to be less than 1 % in all batches. Thus the tablets prepared were found to be good quality and fulfilling all the official requirements of compressed tablets.

The dissolution profile of various tablets formulated employing physical mixture (F1), aceclofenac- PVP40 dispersions (F2) and marketed tablet were shown in table 56. Tablets formulated with solid dispersions gave rapid dissolution of the medicament when compared to the tablets formulated employing physical mixture. The dissolution of medicament from all tablets followed first order kinetics. The dissolution rate was found to be high in the case of tablets formulated employing solid dispersions indicating rapid and higher dissolution of the medicament from these tablets when compared to the tablets formulated with physical mixture.

SUMMARY AND CONCLUSION

Studies were under taken on the preparation and evaluation of solid dispersions of aceclofenac with view to develop fast release formulation of aceclofenac. Four carriers viz PVP10, PVP40, PVP 360 and PVA 8136 were used to prepare the solid dispersions of aceclofenac by solvent evaporation and kneading method at various drug: carrier ratios namely (1:1, 1:3 and 1:9). The solid dispersions prepared were found to be fine and free flowing powders. X-ray diffraction studies revealed that crystalline nature of aceclofenac in pure form was reduced to amorphous form in the dispersions The thermal behavior of aceclofenac-PVP 40 solid dispersion was studied using DSC indicating that aceclofenac has complexed with PVP 40. This phenomenon is indicative of stronger interaction between aceclofenac and PVP 40 in the solid state. Interaction studies like TLC, FTIR indicated no interaction between drug and polymer used.

Results of dissolution studies showed rapid and fast dissolution of aceclofenac from all solid dispersions when compare with pure drug and physical mixture. Good correlation was absorbed between percentage carrier in the solid dispersion and T_{50} and T_{90} values. Among the four carriers PVP 360 gave highest dissolution rate in the drug carrier ratio of 1:9.

The order of dissolution of aceclofenac from various carriers is
PVP 360(KM)>PVP40 (KM)> PVP10 (KM)> PVP40, PVA 8136 (KM)> PVP10, PVA8136 (KM), PVP360 (SE)> PVP10 (SE)> PVP10, PVA 8136 (SE), PVP40, PVA 8136 (SE)> PVP360, PVA 8136 (KM)> PVP40 (SE)> PVP360, PVA 8136 (SE)

Aceclofenac solid dispersion in PVP 40 (1:9) was formulated into tablets with usual additives and the tablets were evaluated for dissolution characteristics .the dissolution of aceclofenac from tablet formulation based on solid dispersion was found to be fast and rapid when compared to physical mixture of drug and marketed tablet.

The additives added have not hindered the dissolution of aceclofenac from solid dispersions. All the tablet formulations based on the solid dispersion fulfilled the official dissolution requirements. Hence the tablet formulations based on solid dispersions are considered as fast release dosage of aceclofenac.

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